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Amygdala-Prefrontal Function and Clinical Course among Adolescents and Young Adults at Clinical High Risk for Psychosis

A dissertation submitted in partial satisfaction of the

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by

Dylan G. Gee

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ABSTRACT OF THE DISSERTATION

Amygdala-Prefrontal Function and Clinical Course among Adolescents and Young Adults at Clinical High Risk for Psychosis

by

Dylan G. Gee

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2015

Professor Tyrone D. Cannon, Co-Chair

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Emotion processing deficits are core features of schizophrenia, and patients display abnormalities in emotion processing at the neural level. However, the extent to which these deficits are present prior to the onset of psychosis and the role that they might play in its development are not well understood. Given the severity of psychotic illness and limitations of extant treatments, research has increasingly focused on the early detection of risk for psychosis to elucidate mechanisms underlying risk progression and facilitate early intervention. Integrating biological markers derived through neuroimaging into predictive algorithms represents a promising avenue to improve risk detection. Based on prior findings of amygdala-prefrontal abnormalities in schizophrenia, the present study investigated whether alterations in amygdala-prefrontal circuitry predate the onset of psychosis and predict clinical outcomes. Participants

were adolescents and young adults at clinical high risk (CHR) for psychosis and healthy controls who completed an emotional faces fMRI task at baseline and received follow-up clinical assessments through the North American Longitudinal Prodrome Study. Findings revealed differential activation and functional connectivity at baseline among CHR participants who recovered symptomatically within six months or who converted to psychosis. Compared with non-converting CHR participants and healthy controls, converters exhibited reduced activation in the amygdala and prefrontal cortex (PFC) during emotion processing. Converters showed positive amygdala-PFC connectivity, compared with the expected pattern of negative connectivity in this regulatory circuit. In contrast, the recovery group resembled controls and showed increased amygdala and PFC activation, as well as stronger negative amygdala-prefrontal functional connectivity. Behaviorally, CHR participants who converted to psychosis also performed with lower accuracy during the emotional faces task at baseline, compared with CHR participants who recovered from the at-risk state. The present findings suggest that the extent to which amygdala-prefrontal circuitry is abnormal or typical among individuals at risk for psychosis may relate to the severity of clinical course. Taken together, these results provide novel insight into the nature of emotion processing deficits in the development of psychosis and may enhance early identification of risk for psychosis.

The dissertation of Dylan G. Gee is approved.

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DEDICATION

For my parents and Andrew, who inspired me to pursue my passions from an early age, who have always believed in me and provided unwavering support, and without whom none of this would have happened.

For Dave, for his love, support, patience, humor, and unparalleled enthusiasm every step of the way.

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Science and everyday life cannot and should not be separated.
Rosalind Franklin

INTRODUCTION

Emotion processing deficits comprise a core domain of disturbance among patients with schizophrenia. Patients exhibit impairment across domains such as emotion perception, expression, and reward anticipation (Barch & Dowd, 2010; Edwards, Jackson, & Pattison, 2002; Fakra, Salgado-Pineda, Delaveau, Hariri, & Blin, 2008; Gard, Kring, Gard, Horan, & Green, 2007; Kohler, Walker, Martin, Healey, & Moberg, 2010; Kring & Moran, 2008). These deficits are often refractory to interventions (Harvey, Patterson, Potter, Zhong, & Brecher, 2006; Penn et al., 2009; Sergi et al., 2007), and they are strongly predictive of poor social and occupational functioning (Hooker & Park, 2002; Irani, Seligman, Kamath, Kohler, & Gur, 2012; Kee, Green, Mintz, & Brekke, 2003; Mueser et al., 1996). Moreover, patients with schizophrenia exhibit structural and functional differences in emotion-related neural circuitry, including altered amygdala activation and weakened amygdala-prefrontal functional connectivity (Anticevic, Van Snellenberg, et al., 2012; Fakra et al., 2008; Gur et al., 2002, 2007; Hempel, Hempel, Schönknecht, Stippich, & Schröder, 2003; Kosaka et al., 2002; Li, Chan, McAlonan, & Gong, 2010; M. L. Phillips et al., 1999; Taylor et al., 2012; Taylor, Phan, Britton, & Liberzon, 2005; Williams et al., 2004, 2007).

Though emotion-related difficulties are core features of schizophrenia and patients display abnormalities in emotion processing at the neural level, the extent to which these deficits are present prior to the onset of psychosis and the role that they might play in its development are not well understood. Given the severity of psychotic illness and limitations of extant treatments, research in the field of psychosis has increasingly focused on the early detection of risk for psychosis with the aims of improving understanding of mechanisms underlying risk progression and disease onset and allowing for early intervention. The development of the clinical high-risk

(CHR) approach has allowed for the study of individuals who exhibit early clinical signs that are predictive of psychosis (reviewed in Fusar-Poli et al., 2013; Gee & Cannon, 2011). Prior research indicates that adolescents and young adults at elevated risk for psychosis display behavioral impairment in some areas of emotion processing (Phillips & Seidman, 2008). However, it remains unclear whether the neural circuitry involved in emotion processing is altered prior to the onset of psychosis and how such pre-existing deficits might predict the clinical progression of illness.

Examining emotion-related neural circuitry in a CHR population provides a unique opportunity for prospective study of psychosis and related emotion deficits. Moreover, given the neurodevelopmental theory that aberrations in typical brain development play a critical role in the onset of psychosis (reviewed in Karlsgodt et al., 2008), the CHR approach allows for the investigation of brain changes during this period of particular relevance to disease progression. Due to the functional disability associated with socioemotional deficits in schizophrenia and challenges to treating them, understanding the sources of emotional impairment in schizophrenia may be critical for improving patients' quality of life. In particular, characterizing the neural substrates of emotional disturbances and their time course in the progression of psychosis (e.g., whether these abnormalities are present prior to the onset of overt psychosis) may provide insight into the physiological substrates of impairment in schizophrenia and their potential role in its development.

Knowledge about emotion processing deficits at the neural level has the potential to inform the development of novel intervention strategies and to identify individuals who might benefit from early intervention targeting emotional functioning. In addition, characterizing alterations in the neural circuitry underlying emotion processing among at-risk patients may

allow for the examination of changes that accompany effective socioemotional interventions in the future, potentially yielding important insight into mechanisms of treatment. Moreover, identifying neural substrates of emotion-related deficits among individuals at CHR for psychosis has the potential to enhance the prediction of illness onset. For example, the continued refinement of criteria for predicting psychosis will likely benefit from the integration of quantitative, objective markers such as brain-based measures. Thus, understanding the timing of onset and neural underpinnings of emotion-related deficits could lead to novel approaches to treatment and prevention of functional disabilities in schizophrenia, as well as more effective identification of risk.

As such, the present research aims to test whether neural abnormalities related to emotion processing predate the onset of psychosis and to examine how such deficits (or lack of deficits) may predict clinical outcomes. Adolescents and young adults at CHR for psychosis and typically developing controls will perform an emotional faces fMRI task, yielding measures of brain activation and functional connectivity. Primary analyses will focus on whether alterations in amygdala-prefrontal circuitry relate to subsequent clinical course. Thus, we will test whether altered amygdala and prefrontal activation or connectivity characterize CHR participants who subsequently convert or recover from the prodromal syndrome, relative to non-converters or non-recoverers, respectively. Given prominent neurodevelopmental models of psychosis, analyses will also test whether the clinical subgroups of the CHR group display altered age-related changes in the relevant neural circuitry. In order to assess the predictive nature of brain function subserving emotion processing, we will examine how pre-existing changes in amygdala-prefrontal circuitry might relate to subsequent clinical course.

A review of background literature will begin with emotion deficits in schizophrenia and at-risk groups to highlight impairment associated with emotion processing in psychosis and potential deficits that may exist prior to illness onset. Studies from basic affective neuroscience focusing on the neural circuitry supporting emotion processing and its development will provide knowledge about the relevant systems that may be disrupted in psychosis. Finally, investigations of the neural bases of emotion deficits in schizophrenia and the neurodevelopmental nature of the disorder will lead into the review of what is known to date about neural circuitry in individuals at elevated risk for psychosis.

Emotion Processing as a Core Deficit in Schizophrenia

Socioemotional functioning represents a core deficit in schizophrenia, with emotion processing identified as a domain of social cognition that is particularly relevant to schizophrenia (Green et al., 2008). A wealth of evidence demonstrates that emotion processing is impaired in schizophrenia, suggesting that the neural circuitry subserving emotion processing may be of particular interest for understanding functioning and disease progression. Disturbances in emotion have long been considered core features of schizophrenia (Bleuler, 1950; Kraeplin, 1971), and patients with schizophrenia show abnormalities across various domains of emotional processing (e.g., perception, expression) (Fakra et al., 2008; Kohler et al., 2010; Kring & Moran, 2008). Alterations in these processes significantly interfere with functioning and social interaction, diminishing quality of life for patients with schizophrenia.

Extant research has consistently identified deficits in emotion recognition among patients with schizophrenia, with large effect sizes relative to controls (Chan, Li, Cheung, & Gong, 2010; Edwards et al., 2002; Green et al., 2011; Kohler et al., 2010; Kring & Moran, 2008). Emotion

recognition tasks typically involve selecting an emotional label that describes a target facial expression of emotion (identification) or making a judgment about differences between two facial expressions of emotion (discrimination). Patients show impaired performance across affect identification and discrimination tasks (Kohler et al., 2010), and impairment across modalities (i.e. facial affect recognition and emotional prosody identification) (Edwards et al., 2002). Despite consistent findings of decreased emotion recognition abilities in schizophrenia, some researchers have questioned whether these findings reflect a specific emotion processing deficit or a more general deficit in basic face processing. For example, patients with schizophrenia also exhibit impairment on tasks of identity recognition, suggesting a more generalized deficit (e.g., Kerr & Neale, 1993). However, various studies have observed evidence for a specific impairment in emotion processing, over and above a facial processing deficit. For example, patients display greater relative impairment when processing emotional information from faces, compared with information such as gender or age (Gooding, Luh, & Tallent, 2001). In addition, patients exhibit greater deficits when processing emotional compared with neutral faces (Hooker & Park, 2002; Norton, McBain, Holt, Ongur, & Chen, 2009).

Deficits in emotion processing have substantial consequences, as they interfere with functioning on a broader scale. Indeed, these deficits are strongly related to impairment in social and community functioning, both contemporaneously and prospectively (Hooker & Park, 2002; Irani et al., 2012; Kee et al., 2003; Mueser et al., 1996). For example, impaired emotion recognition has been linked with diminished social competence among patients with schizophrenia (Mueser et al., 1996), and impaired performance on an affect matching task related to poorer communication and occupational dysfunction (Hooker & Park, 2002). Moreover, emotion perception ability has been shown to predict later independent living and occupational

functioning (Kee et al., 2003). A meta-analysis examining the effects of emotion perception on functioning demonstrated significant effects on social problem solving, social skills, and community functioning (Irani et al., 2012). Difficulties in socioemotional processing may manifest as difficulties with school attendance, ability to hold a job, parenting, and maintaining relationships (Häfner et al., 1994; Mueser & McGurk, 2004). As such, continued emotional disturbances may be one of the reasons why patients with schizophrenia often experience functional impairment even after positive symptoms have been treated with medications (J. Addington & Addington, 1998).

Emotion-related deficits are generally refractory to pharmacological interventions. In particular, studies have found limited effects of antipsychotic medications on measures of social cognition, including emotional processing (Harvey et al., 2006; Penn et al., 2009; Sergi et al., 2007). While deficits in social cognition are difficult to treat with medication, efforts to alleviate impairment in novel ways have shown promise for improving social cognition in schizophrenia. Specifically, a meta-analysis of social cognitive training in schizophrenia has demonstrated moderate to large effects of training on facial affect recognition, with some evidence for generalization to symptoms and functioning (Kurtz & Richardson, 2012). In addition, administering oxytocin to patients with schizophrenia has been show to improve social cognition, including performance on emotion perception tasks (Averbeck, Bobin, Evans, & Shergill, 2011; Davis et al., 2013; De Berardis et al., 2013; Fischer-Shofty et al., 2013; Pedersen et al., 2011). Though promising, additional research is needed to better understand these interventions and their dissemination. Evidence that traditional interventions for schizophrenia do not enhance emotion-processing abilities suggests that emotion-related deficits continue to have a major influence on functioning.

The challenges of alleviating socioemotional deficits and their broad impact on functioning highlight the need for enhanced understanding and novel intervention strategies related to emotion processing impairment in schizophrenia. However, little is known about when emotional deficits begin and their time course throughout the progression of risk for psychosis. Moreover, studies of emotion processing in schizophrenia are subject to confounds such as chronicity of illness and antipsychotic medication use. Thus, prospective data is of great importance for understanding the sources and temporal nature of emotional impairment in schizophrenia.

Emotion Processing Deficits in Clinical High Risk Syndrome

Despite widespread socioemotional impairment in schizophrenia, the extent to which such deficits are present prior to the onset of overt psychosis, and the role that they might play in its development, remain unclear. The benefits of prospective research, combined with the severity of psychotic illness and limitations of extant treatments, have contributed to the development of the CHR approach to studying psychosis. Through systematic, empirically validated criteria for identifying individuals at elevated risk for psychosis, the CHR approach has provided unique opportunities for the examination of emotion processing prior to the onset of psychosis.

Research has begun to examine emotion processing among individuals who are at risk for psychosis, providing critical insight into emotion-related behavior prior to overt psychotic illness. Alterations in various domains of emotion processing have been demonstrated across several populations that are at elevated risk for psychosis, namely individuals at CHR for psychosis, at familial high risk for psychosis, and with schizotypal traits. Among the most

commonly observed abnormalities in these at-risk groups are reduced emotion perception, increased anhedonia, and higher levels of negative affect (Phillips & Seidman, 2008). In addition, there is evidence that social functioning, which closely relates to emotion processing, has important predictive value among at-risk populations. For example, social and emotional deficits have been observed prior to psychosis onset, and measures of social cognition have been shown to better predict social functioning than measures of non-social cognition in patients with schizophrenia (Sergi, Rassovsky, Nuechterlein, & Green, 2006). In addition, greater social impairment has been shown to contribute uniquely to the prediction of conversion to psychosis among CHR individuals (Cannon et al., 2008).

Deficits in emotion recognition have been demonstrated among CHR adolescents and young adults (J. Addington, Penn, Woods, Addington, & Perkins, 2008; Amminger et al., 2011; Green et al., 2011; H. S. Kim et al., 2010; van Rijn et al., 2011). For example, CHR individuals displayed impaired performance on a facial affect identification task relative to controls, performing similarly to patients with schizophrenia; however, performance on an affect discrimination task did not differ between the CHR group and healthy controls (J. Addington et al., 2008). Recent research suggests that impairment in facial affect recognition may be a marker of vulnerability to psychosis but does not differ between converters and non-converters (J Addington et al., 2012). Deficits in emotion recognition have also been demonstrated across modalities, with evidence for impairment in both facial and vocal modalities (Amminger et al., 2011). In addition to difficulty recognizing others' emotions, CHR individuals also display decreased awareness of their own emotions (Van Rijn et al., 2011).

Though research on other domains of emotion processing is limited among CHR individuals, some evidence suggests that individuals at CHR for psychosis experience increased

levels of negative emotion, including anxiety, depression, and social phobia (Chudleigh et al., 2011; Meyer et al., 2005). In one study, CHR individuals who experienced particularly negative emotional states during initial psychosis were more likely to develop subsequent exacerbation of psychotic symptoms (Krabbendam & Van Os, 2005). In addition, emotional expression may be altered prior to the onset of psychosis, as prior research has identified flattened affect and disturbances in intonation and communication gestures among CHR individuals (Häfner et al., 2003). Efforts to understand the physiological sources of these early emotion deficits will rely heavily on affective neuroscience research characterizing the neural systems supporting emotion processing.

Neural Circuitry Supporting Emotion Processing

Among neurotypical adults, emotion perception and the detection of salient social stimuli (e.g., facial expressions) depend on networks involved in emotion processing and general face processing. Numerous studies have demonstrated that the amygdala plays a critical role in emotional learning and responds to stimuli of biological relevance including emotional expressions, ambiguity, and salience (Adolphs, Tranel, Damasio, & Damasio, 1994; H. Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Whalen, 1998). The amygdala has been shown to be particularly sensitive to signals of threat (e.g., fearful faces), while also responding to non-threatening stimuli such as neutral and happy faces (Kesler-West et al., 2001; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Whalen et al., 2001). The perception of emotional stimuli occurs through conscious and non-conscious processing. For example, during a backward masking paradigm, the amygdala responded to masked fearful faces even in the absence of explicit knowledge that fearful faces had been presented (Whalen et al., 1998). Through such

automatic evaluation of salient stimuli, the amygdala may play a critical role in coordinating neurophysiological responses by biasing cognition toward perceived stimuli with potential emotional significance (Adolphs, 2003; LeDoux, 2000; Vuilleumier & Pourtois, 2007).

General face processing relies on the inferior occipital gyrus, lateral fusiform gyrus, and posterior superior temporal sulcus (STS) (Halgren et al., 1999; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Belger, & Allison, 1999). Specifically, it is thought that the fusiform gyrus processes invariant aspects of faces (e.g., unique identity) while the STS processes changeable aspects of faces (e.g., eye gaze, expression) (Haxby, Hoffman, & Gobbini, 2000). In addition, some models have emphasized the importance of connectivity between these regions (Haxby et al., 2000) and an extended network including the amygdala, hippocampus, inferior frontal gyrus, and orbitofrontal cortex (OFC) (Ishai, Schmidt, & Boesiger, 2005). The medial prefrontal cortex (mPFC) and STS have also been implicated as representing emotions at a more integrated, abstract level and extracting meaning from emotional faces (Peelen, Atkinson, & Vuilleumier, 2010). A recent meta-analysis of networks involved in processing emotional faces highlighted the importance of the amygdala, which was one of the areas most commonly observed across studies (Sabatinelli et al., 2011).

Interactions between subcortical (e.g., amygdala) and cortical (e.g., PFC) regions are fundamental to the processing and regulation of emotional reactivity (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Kim et al., 2003; Lieberman et al., 2007). While the amygdala generates emotional signals in the brain, its connections with PFC enable regulation of those signals. Thus, while attention to emotion can be biased through bottom-up processes driven by the amygdala and subcortical structures, reactivity is thought to be modulated through top-down cognitive control (Ochsner, Bunge, Gross, & Gabrieli, 2002). Human neuroimaging studies of adults

(Johansen-Berg et al., 2008; Kim & Whalen, 2009) have revealed the presence of both structural and functional connections between the amygdala and mPFC (including OFC and ventral anterior cingulate cortex (ACC)) that have been identified in animal models (Amaral, Price, Pitkanen, & Carmichael, 1992; Ghashghaei, Hilgetag, & Barbas, 2007). While the specific region of PFC varies by the process, mPFC (H. Kim et al., 2003; Pezawas et al., 2005; Hare et al., 2008) and ventrolateral PFC (e.g., Lieberman et al., 2007) are thought to be particularly important for regulating amygdala activation. Due to a lack of direct anatomical connections between lateral prefrontal regions and the amygdala, it is thought that ventrolateral PFC regulates the amygdala via mPFC (e.g., Lieberman et al., 2007). The vmPFC likely regulates activity of the amygdala through input to the basolateral nuclei of the amygdala and the intercalated cells, which inhibit amygdala activity by regulating inputs from the basolateral nuclei to the central nucleus (Milad & Quirk, 2002; Harris & Westbrook, 1998; Akirav, Raizel, & Maroun, 2006; reviewed in M. J. Kim, Loucks, et al., 2011). These subcortical-cortical interactions are fundamental to the regulation of emotional reactivity during intentional processes such as cognitive reappraisal (Ochsner et al., 2002) as well as incidental processes such as affect labeling (Lieberman et al., 2007).

During a widely used affect labeling and matching task, participants were asked to choose the affective word label that best described a target emotional expression (linguistic processing; *affect labeling*) or to choose the face that matched a target emotional expression (perceptual processing; *affect matching*). Affect labeling increased ventrolateral PFC activation and reduced amygdala activation, compared with affect matching (Hariri, Bookheimer, & Mazziotta, 2000). Building upon this work, Lieberman and colleagues (2007) employed control conditions of gender labeling and gender matching to demonstrate that the inverse pattern of

activation between amygdala and ventrolateral PFC was specific to affect labeling. The relationship between increased right ventrolateral PFC activation and decreased amygdala activation was mediated by mPFC (Lieberman et al., 2007). In addition, affect labeling has been associated with physiological reductions in skin conductance (Tabibnia, Lieberman, & Craske, 2008) and decreases in self-reported distress (Lieberman, Inagaki, Tabibnia, & Crockett, 2011). By contrast to reduced emotional reactivity associated with affect labeling, affect matching increases amygdala reactivitiy (e.g., Hariri et al., 2000; Lieberman et al., 2007). Thus, for the purposes of the present study, brain activation and connectivity will be measured with fMRI during the affect labeling and matching task (Hariri et al., 2000; Lieberman et al., 2007) due to consistent demonstration that it can be used to probe amygdala-prefrontal circuitry. The investigation will primarily focus on amygdala function (targeted with affect matching) and ventrolateral PFC and mPFC function (targeted with affect labeling).

Neural Bases of Emotion Processing Deficits in Schizophrenia

Substantial evidence exists for alterations in the neural circuitry subserving emotion processing among patients with schizophrenia. Consistent with well-established prefrontal abnormalities in schizophrenia (Cannon et al., 1998; Pantelis et al., 2003; Weinberger, Aloia, Goldberg, & Berman, 1994) and the important role of PFC in networks that support emotion processing (reviewed in Monk et al., 2008), it might be expected that patients would exhibit deficits in emotion regulation and alterations in relevant circuitry. Moreover, because social cognition and emotion processing rely on the integration of distributed regions, these networks are likely to be affected by the widespread disconnectivity that is evident in schizophrenia (Lawrie et al., 2002; Lim et al., 1999; Meyer-Lindenberg, 2001; Weinberger et al., 1994).

Indeed, various studies of patients with schizophrenia have observed abnormalities in the structure of regions involved in emotion processing, specifically observing reduced volume in regions such as PFC, amygdala, hippocampus, temporal regions and cingulate cortex (Andreasen et al., 1994; Byne et al., 2002; Nelson, Saykin, Flashman, & Riordan, 1998; Pantelis et al., 2003; Pfefferbaum & Marsh, 1995). In addition, frontotemporal interactions are likely impaired in schizophrenia, and evidence suggests that frontal and temporal volumes may be reduced to a greater extent than posterior regions (Cannon et al., 1998). There is also evidence for related abnormalities among regions within emotion processing networks. For example, decreased prefrontal white matter volumes correlated with amygdala and hippocampal volumes (Breier et al., 1992), and decreased prefrontal activation was associated with greater hippocampal pathology (Weinberger, Berman, Suddath, & Torrey, 1992) among patients. In addition, a meta-analysis of structural abnormalities associated with illness duration suggests that progressive gray matter loss in schizophrenia relates to regions functionally associated with emotion and language (Nickl-Jockschat et al., 2011). Overall, disconnectivity among brain regions has been associated with negative symptom severity (Szeszko et al., 2007).

Consistent with observed neuroanatomic abnormalities (i.e. reduced structural volume) in the amygdala, patients with schizophrenia exhibit alterations in amygdala function. In particular, neuroimaging studies employing emotional stimuli have consistently observed decreased amygdala activation among patients with schizophrenia (Fakra et al., 2008; Gur et al., 2002, 2007; Hempel et al., 2003; Kosaka et al., 2002; M. L. Phillips et al., 1999; Taylor et al., 2005; Williams et al., 2004, 2007). Recent meta-analyses have also identified reduced activation of the amygdala among patients with schizophrenia (Anticevic, Van Snellenberg, et al., 2012; Li et al., 2010; Taylor et al., 2012). In particular, Li and colleagues (2010) observed reduced amygdala

activation across studies of facial emotion. Similarly, Anticevic and colleagues (2012) reported reduced amygdala activation for emotional versus neutral stimuli, though the search space for this meta-analysis was limited to the amygdala. Most recently, Taylor and colleagues (2012) conducted a whole-brain meta-analysis and reported that hypoactivation of the amygdala was one of the most robust findings in neuroimaging studies of emotion perception in schizophrenia. Such hypoactivation appears to be consistent across tasks of varying degrees of complexity, as the effect was present even after tasks were matched on difficulty. Their findings suggested that reduced amygdala activation is particularly apparent in patients during implicit emotion processing (when affective stimuli are processed in the absence of explicit attention to affective features) but is also present during explicit emotion processing (when attention is directed to an emotional expression or characteristic of the face). In addition, patients display hypoactivation in other regions related to emotion processing, such as hippocampus, insula, and ACC (Gur et al., 2002; Taylor et al., 2005). Altered recruitment of these structures in the presence of comparable task performance relative to controls (e.g., Gur et al., 2002), suggests that hypoactivation within networks subserving emotion processing may be a core deficit present in schizophrenia.

Consistent with the conceptualization of schizophrenia as a disorder of disconnectivity (Lawrie et al., 2002; Lim et al., 1999; Meyer-Lindenberg, 2001; Weinberger et al., 1994), patients show decreased functional connectivity of the amygdala and PFC during emotion processing (Anticevic, Repovs, & Barch, 2012; Fakra et al., 2008). During the same task that will be employed in the present study, patients exhibited decreased negative functional connectivity between the amygdala and PFC, suggesting a failure to recruit regulatory brain regions during incidental emotion regulation (Fakra et al., 2008). In addition, while patients and controls exhibited similar activation patterns during affect labeling, patients showed decreased

amygdala activation during affect matching. Patients also exhibited decreased activation of regions involved in holistic face processing (e.g., fusiform gyrus) and increased activation of regions associated with feature analysis (e.g., temporal lobe, precuneus), suggesting that patients might use a more feature-based approach to face processing. While limited research on incidental emotion regulation has been conducted among patients with schizophrenia, decreased amygdala, mPFC, and ACC activation and increased arousal were observed during implicit emotion processing (gender judgments), suggesting altered regulatory function even during implicit tasks (Williams et al., 2004). Furthermore, neuroimaging studies of emotion in schizophrenia also suggest abnormalities in the amygdala and mPFC related to emotion regulation and the retention of safety cues in fear extinction (Fakra et al., 2008; Holt, Coombs, Zeidan, Goff, & Milad, 2012).

Recent research has also revealed alterations in default mode network (DMN) function among patients with schizophrenia. The DMN comprises midline structures including mPFC and posterior cingulate cortex (PCC) that exhibit temporally coherent low-frequency fluctuations and are functionally connected while the brain is at rest, and that tend to be deactivated during goal-directed task (Raichle et al., 2001). Research on DMN function in schizophrenia suggests that patients exhibit a failure to disengage from the default mode during task (Guerrero-Pedraza et al., 2012; Hasenkamp, James, Boshoven, & Duncan, 2011; Nygård et al., 2012; Salgado-Pineda et al., 2011; Whitfield-Gabrieli et al., 2009). These findings may point to one potential mechanism by which patients with schizophrenia exhibit altered emotional processing. However, given that the DMN overlaps in part with networks typically associated with social cognition (Amodio & Frith, 2006; Lieberman, 2007; Uddin, Iacoboni, Lange, & Keenan, 2007), it may be difficult to dissociate between task-related and DMN-related abnormalities.

Taken together, neuroimaging studies of schizophrenia suggest alterations in functional activation within networks supporting emotion processing and decreased functional connectivity between subcortical and cortical regions. Whether these abnormalities are a cause or consequence of schizophrenia (or its treatment) is not yet clear. However, because individuals at CHR for psychosis exhibit emotion-related behavioral deficits (J. Addington et al., 2008; H. S. Kim et al., 2010; Phillips & Seidman, 2008; van Rijn et al., 2011) and individuals at CHR for psychosis and those with high psychosis-proneness display alterations in amygdala-prefrontal circuitry (Gee et al., 2012; Modinos, Ormel, & Aleman, 2010), abnormal function in networks subserving emotion processing might predate (and potentially contribute to) psychosis onset.

Neural Bases of Emotional Impairment in Clinical High Risk Syndrome

A major theory of the etiology of schizophrenia posits that aberrations in neurodevelopment play a fundamental role in the emergence of psychosis, underlining the need for prospective investigation of the progression of psychosis (reviewed in Karlsgodt et al., 2008). Psychosis involves risk factors that affect both early and late developmental brain changes (Cannon et al., 2003; McDonald & Murray, 2000). Patients with psychotic disorders display evidence of disruption in these typical processes, particularly with regard to structural maturation. Specifically, theories regarding the etiology of schizophrenia have emphasized the potential role of aberrant synaptic pruning (McGlashan & Hoffman, 2000), which is thought to result in widespread disconnectivity (Weinberger et al., 1994; Lim et al., 1999; Meyer-Lindenberg et al., 2001; Lawrie et al., 2002). Thus, studying the course of dynamic changes during adolescent brain development may provide insight into the onset and progression of psychotic disorders.

Extant research indicates structural brain abnormalities prior to the onset of psychosis, which may relate to emotional disturbances. Among CHR individuals who eventually convert to psychosis, longitudinal studies have observed progressive decreases in gray matter volume in superior temporal and prefrontal regions (Borgwardt et al., 2007; Pantelis et al., 2003; Sun et al., 2009; Takahashi et al., 2009). For example, in a longitudinal study of individuals at CHR for psychosis, those who later converted to psychosis exhibited reduced gray matter volume in right medial temporal, lateral temporal, inferior frontal cortex, and bilateral cingulate cortex, relative to non-converters. Moreover, when scanned at a follow-up period of twelve months or greater, those who developed psychosis demonstrated longitudinal changes of reduced gray matter volume in left parahippocampal, fusiform, OFC, cerebellum, and cingulate gyri, whereas non-converters did not display longitudinal change in any regions except for cerebellum (Pantelis et al., 2003). Consistent with prior results, CHR individuals displayed reduced gray matter volume in cingulate gyrus, right inferior frontal gyrus, superior temporal gyrus, and hippocampus, relative to controls (Witthaus et al., 2009). Amygdala volumes have been observed to be normal among CHR groups (Velakoulis et al., 2006; Witthaus et al., 2010) despite evidence for reduced amygdala volume in first-episode patients (Witthaus et al., 2009). Results on hippocampal volume have been mixed, with some evidence for reduced volume (Witthaus et al., 2010) and normal volume (Velakoulis et al., 2006) among CHR individuals. Given the role of these regions in emotion processing, structural abnormalities would suggest that CHR individuals may also exhibit changes in brain function prior to conversion to psychosis.

Neuroimaging studies of brain function among CHR individuals have been limited; however, initial evidence suggests that the neural circuitry supporting emotion processing is disrupted prior to psychosis onset. A preliminary study of individuals at CHR for psychosis

demonstrated altered age-related patterns of amygdala and prefrontal activation during emotion processing (Gee et al., 2012). Specifically, controls exhibited increased prefrontal activation and decreased amygdala reactivity with age, whereas CHR participants exhibited decreased prefrontal activation and amygdala hyperreactivity with age. In addition, the CHR group showed weaker amygdala-prefrontal functional connectivity. However, this multisite pilot study was based on a small sample, and it is unclear whether results will replicate across the larger NAPLS sample. Moreover, research has yet to elucidate whether such early alterations might predict subsequent clinical outcomes. In a study of individuals selected for high psychosis proneness (PP) and low PP, the high PP group showed heightened prefrontal activation and a lack of reduction in amygdala activation during a reappraisal task (Modinos et al., 2010). Moreover, weaker functional connectivity between the amygdala and PFC was found in the high PP group. Taken together, these preliminary studies suggest that disturbances in amygdala and prefrontal activation may predate the onset of psychosis and underlie emotion-related deficits observed in individuals at risk for psychosis.

Present Research: Aims and Hypotheses

Given substantial impairment related to emotional deficits in schizophrenia, delineating the timing of onset and neural underpinnings of emotion-related abnormalities among individuals at CHR for psychosis may provide critical insight into sources of deficits, novel socioemotional interventions, and identification of risk for functional disability in schizophrenia. As such, the present research aims to test the theory that deficits in emotion-related neural circuitry exist prior to the onset of psychosis and that the severity of such deficits may predict the clinical course of psychotic illness. As part of the North American Prodrome Longitudinal Study (NAPLS),

adolescents and young adults at CHR for psychosis and typically developing controls between the ages of 12-33 participated in an fMRI study and clinical assessments at 6-month follow-up intervals to examine illness progression. The emotional faces fMRI task yielded measures of amygdala and prefrontal activation and functional connectivity. In addition, the task conditions allowed for the examination of explicit emotion processing (i.e., affect labeling and affect matching) and implicit emotion processing (i.e., gender labeling and gender matching).

Between-group analyses of behavioral performance and brain function allowed for the examination of abnormalities in neural circuitry associated with the CHR state. Given the neurodevelopmental nature of schizophrenia, analyses examined whether clinical course was associated with differences in age-related brain function among CHR participants. In order to examine whether baseline measures of brain activation and functional connectivity predicted the progression of psychosis, analyses tested whether the extent of changes in amygdala-prefrontal circuitry at baseline was associated with the severity of clinical course.

Aim 1: To test the theory that pre-existing physiological deficits in emotion processing circuitry predate the onset of psychosis and characterize individuals at risk for psychosis who later develop psychosis.

Hypothesis 1A: CHR participants who subsequently convert to psychosis will exhibit decreased amygdala and prefrontal activation during emotion processing, relative to controls and non-converting CHR participants.

Hypothesis 1B: CHR participants who subsequently convert to psychosis will exhibit reduced functional connectivity between the amygdala and prefrontal cortex, relative to controls and non-converting CHR participants.

Hypothesis 1C: CHR participants who subsequently convert to psychosis will exhibit decreased prefrontal and amygdala activation and weaker functional connectivity with age, relative to controls and non-converting CHR participants.

Aim 2: To test the model that less severe deficits among individuals at risk for psychosis predict a better clinical course.

Hypothesis 2A: CHR participants who recover symptomatically during the follow-up period will exhibit amygdala and prefrontal activation that significantly differs from non-recovering CHR participants but not from controls.

Hypothesis 2B: CHR participants who recover symptomatically during the follow-up period will exhibit functional connectivity between the amygdala and prefrontal cortex that significantly differs from non-recovering CHR participants but not from controls.

Hypothesis 2C: CHR participants who recover symptomatically during the follow-up period will exhibit age-related changes in amygdala and prefrontal activation and functional connectivity that significantly differ from non-recovering CHR participants but not from controls.

METHODS

Participants

Participants consisted of 216 CHR adolescents and young adults and 129 healthy controls between 12 and 35 years old. The protocol was approved by Institutional Review Boards at the sites participating in NAPLS, from which participants were drawn (Emory University, Harvard University, University of Calgary, University of California Los Angeles (UCLA), University of

California San Diego, University of North Carolina (UNC), Yale University, Zucker Hillside Hospital), and participants provided informed consent or assent (parental informed consent for minors).

Clinical Measures

Participants were screened using the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001) for the presence of a prodromal syndrome: attenuated subthreshold psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS), substantial functional decline combined with genetic risk for psychosis (GRD), or youth and schizotypy (YS). The APS criterion consists of the onset or worsening of subthreshold positive symptoms within the past 12 months. Such symptoms are categorized into unusual thought content, suspicion/paranoia, perceptual abnormalities, grandiosity, and disorganized communication. The severity of each symptom type is rated based on its frequency, duration, impact on functioning, and extent of loss of insight. Brief intermittent psychotic symptoms (BIPS) constitute a second category of CHR criteria, which refers to the onset of transient suprathreshold psychotic symptoms within the past 3 months. That is, individuals meeting BIPS criteria experience positive symptoms that are of a psychotic intensity level but do not meet criteria for a DSM-IV Axis I psychotic disorder diagnosis. Genetic risk and deterioration (GRD) forms a third category of CHR syndrome, which is identified by genetic risk for psychosis and recent functional decline. GRD criteria have previously been operationalized as having a first-degree relative with a psychotic disorder, or as having a diagnosis of schizotypal personality disorder, in addition to a decline in functioning within the past 12 months as measured by the Global Assessment of Functioning (GAF) score (e.g., Cannon et al., 2008). YS refers to

individuals under 18 years of age who meet criteria for schizotypal personality disorder. Of the 216 CHR participants, 90.7% met prodromal criteria based on APS, 6.0% GRD, 2.8% YS, and 0.5% BIPS. Six participants classified as APS also met criteria for another prodromal syndrome (four for APS and GRD; one for APS and YS; one for APS, GRD, and YS).

CHR participants were excluded if they met DSM-IV criteria for an Axis I schizophrenia-spectrum disorder. Control participants were excluded if they met DSM-IV criteria for a psychiatric disorder, had a first-degree relative with a current or past psychotic disorder, or met prodromal criteria. General exclusions included substance dependence (past 6 months), neurological disorder, or Full Scale IQ <70.

Clinical assessments were conducted at baseline, every six months, and following conversion to psychosis. The SIPS was used to assess for prodromal and psychotic symptoms. The Scale of Prodromal Symptoms (SOPS) scale within the SIPS employs a continuous scale (0-6) to measure the severity of symptoms, with 0 indicating the absence of symptom, 1 indicating questionable presence, 2 indicating mild presence, 3-5 indicating moderate to severe in the prodromal range, and 6 indicating overt psychosis. In addition, the SCID-I for DSM-IV-TR and the SCID-II were used for assessment of psychiatric disorders at each assessment. Overall functioning was measured using the Global Assessment of Functioning (GAF) scale, and social and role functioning were assessed using the GAF-Social and GAF-Role scales (Cornblatt et al., 2007).

Current Clinical State

At each follow-up point, a Current Clinical State (CCS) classification was used to indicate the course of symptoms during the past six months, thus providing a measure of symptom change for each participant. The CCS classification accounted for the CHR criteria

(APS, BIPS, GRD, YS) currently met by the participant, as well as ratings of positive symptom severity on the SOPS. The Healthy Control group comprised participants who entered the study as controls and continued to meet criteria for healthy controls. Symptom Recovery comprised participants whose symptoms remitted across the past six months. Specifically, this group did not currently meet CHR criteria and all positive symptom ratings were <3 on the SOPS. Symptom Non-Recovery comprised participants whose symptoms progressed or remained stable, but still remained in the prodromal range, across the past six months. Within the Symptom Non-Recovery group, Prodromal Progression comprised participants who continued to meet one of the CHR criteria, and Symptomatic comprised participants whose CHR criteria were in remission (i.e., they did not currently meet CHR criteria) but who had one or more positive symptoms rated in the 3-5 range on the SOPS in the past four weeks but with no increase in the last year. Conversion comprised participants whose symptoms surpassed the threshold of overt psychosis (a 6 on the SOPS).

Aim 1 compared conversion, non-conversion, and control groups. The non-conversion group included all CHR participants who did not convert to psychosis (i.e., participants who either displayed stable symptoms, displayed worsening symptoms but did not surpass the threshold for psychosis, or recovered symptomatically). Aim 2 compared recovery, non-recovery, and control groups. The non-recovery group included all CHR participants who did not recover (i.e., participants who either displayed stable symptoms, displayed worsening symptoms but did not surpass the threshold for psychosis, or converted to psychosis).

fMRI Task Paradigm

The experimental paradigm consisted of an emotional faces task (Hariri et al., 2000; Lieberman et al., 2007) (Figure 1). Participants viewed target faces or shapes while performing one of five tasks in each block. Affect labeling involved choosing which of two labels (e.g., "angry," "happy," "scared," "surprised") described a target face. Gender labeling involved selecting the gender-appropriate name for a target face. Affect matching involved choosing which of two faces displayed the same emotion as a target face. Gender matching involved selecting which of two faces was the same gender as a target face. Shape matching involved selecting which of two shapes was the same as a target shape.

Each block began with a 3-second instruction cue to indicate the task condition, followed by 10 trials of that task, randomly selected from a pool of trials. Each trial was 5 seconds in length. Thus, each block was 50 seconds long. Blocks were separated by a 10-second fixation crosshair. The order of blocks was randomly selected for each participant. Participants completed two functional runs, with each condition type occurring once per run. Responses were registered using a button box, and participants were told to respond as soon as they were sure of the correct answer. The stimuli remained on the screen for the entire 5-second duration of each trial.

Facial stimuli were chosen from a standardized set (Tottenham et al., 2009). Half of the target faces in each condition were female and half were male. The target face depicted a negative emotional expression (i.e., fear or anger) in 80% of the trials comprising each condition. In the other 20% of trials, the target face consisted of a happy or surprised face. The affect labels and gender names were matched on a number of dimensions (same number of words, word length; for each affect label, there was a name that began with the same letter in the gender label condition).

Affect labeling is considered to represent a form of incidental emotion regulation (Lieberman et al., 2007) and has been associated with increased activation in ventrolateral PFC and dampening of amygdala activation, as well as decreases in negative emotion and reduced physiological responsivity (Lieberman et al., 2011; Tabibnia et al., 2008). By contrast, affect matching has been associated with increased amygdala activation, relative to affect labeling. For these reasons, we focused on affect labeling and matching to probe amygdala-prefrontal circuitry in the present study. Based on findings on multi-site reliability suggesting that comparing a given condition to implicit baseline may increase reproducibility of results (Gee et al., in press), affect labeling and affect matching were compared to implicit baseline.

When findings were significant for either affect labeling (versus implicit baseline) or affect matching (versus implicit baseline), higher-order contrasts were conducted to clarify the specificity of the result. Contrasts of affect labeling and affect matching to appropriate control conditions were based on prior work (Lieberman et al., 2007). The affect conditions were compared with the gender conditions to test the specificity of a finding. For example, the affect versus gender contrast allowed for a test of explicit (when attention is directed to affective features of stimuli; e.g., affect labeling or affect matching) versus implicit (when participants view affective stimuli but attention is not directed to affective features; e.g., gender labeling or gender matching) emotion processing. Prior evidence suggests that labeling is a stronger test of prefrontal function given increased prefrontal activation associated with labeling (Lieberman et al., 2007). In addition, matching is considered to be a stronger test of amygdala function given more robust activation to matching as well as the dampening of amygdala that is associated with labeling. Therefore, higher-order contrasts for results in prefrontal cortex focused on a comparison of affect labeling with gender labeling, whereas higher-order contrasts for results in

the amygdala focused on a comparison of affect matching to gender matching. When appropriate, affect labeling was compared to affect matching to test whether an effect was stronger for the process of labeling or matching.

Functional Imaging Parameters

Scanning was performed on Siemens Trio 3.0 Tesla (3T) scanners (Emory University, Harvard University, UCLA, Yale University), a Siemens Allegra 3T scanner (UNC), and GE 3T scanners (UCSD, University of Calgary, Zucker Hillside Hospital). A standard radiofrequency head coil was employed. Anatomical reference scans were acquired to configure slice alignment. A T2-weighted image (0.9-mm in-plane resolution) was acquired using a set of high-resolution echo planar (EPI) localizers (Siemens: TR/TE 6310/67ms, 30 4-mm slices with 1-mm gap, 220-mm FOV; GE: TR/TE 6000/120ms, 30 4-mm slices with 1-mm gap, 220-mm FOV). Functional scans matched the AC-PC aligned T2 image and utilized an EPI sequence (TR/TE 2500/30ms, 77 degree flip angle, 30 4-mm slices). Each functional run consisted of 129 volumes.

Image Processing: Functional Activation

Functional image analysis was performed using FSL (FMRIB's Software Library v. 4.0) (Smith et al., 2004). Motion in EPI data was corrected using a six-parameter, rigid-body 3D co-registration (FLIRT), which registered each BOLD image to the middle data point in the timeseries. Data were registered for each participant (EPI to participant's T2-weighted structural image, then T2 to standard space brain) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson M. & Smith S., 2001). Data were spatially smoothed with a 5-mm (FWHM) Gaussian kernel and

filtered with a non-linear high-pass filter (120s cut-off). Individual participant analyses employed FEAT (FMRI Expert Analysis Tool).

Timeseries statistical analysis on each participant was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. A univariate general linear model (GLM) was applied on a voxel-by-voxel basis such that each voxel's timeseries was individually fitted to the resulting model, with local autocorrelation correction applied within tissue type to improve temporal smoothness estimation (Woolrich, Ripley, Brady, & Smith, 2001). Each voxel's goodness-of-fit to the model was estimated; resulting parameter estimates indicated the degree to which signal change could be explained by each model. Each condition was modeled separately, with each correct trial modeled in its entirety in a block design fashion. Motion parameters were entered as covariates; volumes with motion >3mm were excluded. Resulting contrast images were entered into second-level analyses (fixed effects model) to combine functional runs for each participant and to allow for inferences at the group level. Second-level contrast images that combined the two runs for each participant were subsequently entered into group-level analyses. Fourteen participants (4 controls, 5 non-converters, 5 converters) completed only one run of the task and were thus excluded from group-level analyses.

Group-level analyses of whole brain activation were conducted in FSL. Group analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects), and FLAME 1+2 was used due to the small sample size in the conversion group (Behrens et al., 2003; Smith et al., 2004). Each participant's data, including parameter and variance estimates for each contrast from the lower-level analysis, were entered into a GLM in FSL. Correction for multiple comparisons was applied at the cluster level within a priori regions of interest following Monte Carlo simulations conducted in the AlphaSim program within AFNI. AlphaSim was conducted across

the whole brain with 10,000 simulations at 6mm FWHM and an individual voxel threshold of .05. The minimum number of contiguous voxels necessary to achieve $p<.01$ was 230; the minimum number of contiguous voxels necessary to achieve $p<.05$ was 187. Given that hypotheses regarding functional connectivity focused on amygdala connectivity with prefrontal cortex, the search space for PPI analyses was limited to frontal regions. The search space was defined using a mask comprised of all frontal regions in the Harvard-Oxford Structural Atlas (Kennedy et al., 1998; Makris et al., 1999). Voxels with atlas-derived values corresponding to a $\geq$25% probability of belonging to the given region were included. Correction for multiple comparisons in PPI analyses was conducted with the same algorithm in AlphaSim within the specified volume of the frontal mask. The minimum number of contiguous voxels necessary to achieve $p<.05$ was 93. All coordinates for peak voxels are reported in MNI space.

The group-level GLM analyses tested whether the groups differed on functional activation across the whole brain for each contrast of interest (affect labeling > baseline, affect matching > baseline; higher-order contrasts with control conditions when appropriate). The GLM for each contrast modeled each group while controlling for age (demeaned) and sex (demeaned). Site was also included as a covariate of non-interest in all group-level analyses. Prior research suggests that including site as a covariate in group-level GLMs produces comparable results to an image-based meta-analytic approach that combines effects across individual sites (Gee et al., in press). In order to illustrate the main findings, percent signal change (for activation) or beta weights (for PPI) were extracted for clusters of voxels that represented group differences. The masks used to extract the values were defined based on the entire cluster, except when the primary region was part of an extensive cluster spanning other regions. In that case, definition of

the mask is described in the corresponding figure caption. Plots of the extracted values were created for illustration purposes only; statistical analyses were not repeated.

Functional Connectivity

A PPI analysis (Friston et al., 1997) was conducted to examine whether task-dependent functional connectivity between the amygdala and prefrontal regions differed between groups. That is, the PPI analysis tested whether groups differed on the extent to which the amygdala covaried with other brain regions more during one condition than another. For each participant, a first-level GLM analysis was carried out in FSL on the preprocessed first-level data with regressors for task, seed region timeseries, and the interaction of task and timeseries. The psychological (task condition) regressor modeled whether a given trial consisted of affect labeling or the control condition for the given analysis. The physiological (seed region timeseries) regressor comprised the timeseries for the amygdala. A third regressor modeled the interaction of the psychological regressor and the physiological regressor, such that it identified regions that covaried in a task-dependent manner with the amygdala (e.g., regions that significantly correlated more with the amygdala during affect labeling than during implicit baseline). Six motion regressors were included in the first-level analysis for each participant. As in the prior analyses of functional activation, a second level analysis combined results from the first and second run for each participant. Group-level analyses examined differences between groups in terms of regions that significantly covaried with the amygdala more during emotion processing than a control condition. The PPI group analyses were conducted in FLAME (Behrens et al., 2003; Smith et al., 2004) with correction for multiple comparisons in frontal

regions using AlphaSim. The PPI analysis was conducted for left and right amygdala seeds, given evidence for differential connectivity in prior work (Fakra et al., 2008).

Regions of Interest

Based on prior work (Lieberman et al., 2007), the amygdala and ventrolateral PFC were selected as regions of interest (ROI) for use in secondary analyses. Anatomically defined masks for the left and right amygdala and inferior frontal gyrus (including ventrolateral PFC) were defined using the Harvard-Oxford Structural Atlas (Kennedy et al., 1998; Makris et al., 1999). Voxels with atlas-derived values corresponding to a ≥25% probability of belonging to the given region were included. FSL's Featquery was used to warp ROIs back into each participant's space by applying the inverse of the transformation matrix used during the initial registration. The motion-corrected, smoothed, and filtered data were probed for mean percent signal change.

A between-subjects repeated measures ANOVA was conducted on amygdala activation (mean percent signal change in right anatomical ROI; relative to implicit baseline) to establish a reference for the overall pattern of amygdala activation in the present sample, which would aid in interpreting between-group results and higher-order contrasts. The between-subjects factor was group (control, CHR) and the within-subjects factor was condition (affect labeling, affect matching, gender labeling, gender matching, shape matching).

Clinical Course: Conversion and fMRI Measures (Aim 1)

Participants whose symptoms surpassed the threshold of overt psychosis (a 6 on the SOPS) at any time during the study were classified as converters for the purposes of testing Aim 1. The GLM for each task contrast modeled group (controls, non-converters, converters) while

controlling for age, sex, and site. Contrasts focused on group differences and group x age interactions. Specifically, the analysis allowed for examination of an interaction by producing statistical maps of regions for which activation or connectivity differed between groups in terms of whether it increased, decreased, or did not significantly change with age. For example, the analysis would identify regions for which activation or connectivity increased for patients while decreasing with age for controls, or vice versa.

Because five of the fourteen converters completed only one run of the task, analyses of whole-brain data for Aim 1 included nine converters. Thus, secondary analyses were conducted using ROI data that allowed for inclusion of all fourteen converters in order to verify whether results were similar with the entire conversion sample.

Clinical Course: Recovery and fMRI Measures (Aim 2)

For the purposes of testing Aim 2, participants were classified as controls, recovery, or non-recovery based on their CCS rating at follow-up. Participants who were controls or in the recovery group were classified as such; participants who were classified as Prodromal Progression, Symptomatic, or Conversion were aggregated to form the non-recovery group. Following the procedures for image processing described above, group-level analyses examined whether functional activation and functional connectivity differed at the baseline MRI scan depending on participants' subsequent clinical course over the follow-up period (CCS: recovery, non-recovery, control). Similar to the design for Aim 1, the GLM for each task contrast modeled three groups, age, and sex. Contrasts of interest focused on whole-brain group differences and group x age interactions for the recovery, non-recovery, and control groups. Sixteen participants

were lost to follow-up following the MRI scan, thus these 16 participants did not have CCS classifications and were excluded from the Aim 2 analyses.

Demographic and Behavioral Data Analysis

Between-subjects (group: controls, non-converters, converters for Aim 1; controls, non-recovery, recovery for Aim 2) repeated-measures (affect labeling, affect matching, gender labeling, gender matching, shape matching) ANOVA was performed to test for main effects of group and condition, as well as their interaction, on behavioral performance. The primary measures of behavioral performance were accuracy (% correct out of all responded trials) and mean reaction time (RT). Correlational analyses were used to test whether age was associated with performance. Participants were excluded due to poor behavioral performance if they responded to <50% of trials, resulting in the exclusion of one participant from the CHR conversion group. The excluded participant was also removed from all analyses due to a lack of sufficient trials to model the fMRI data.

Default Mode Network: Secondary Analyses

To rule out the possibility that primary results may have been influenced by group differences in DMN function, secondary analyses were conducted to test for group differences in DMN activity and connectivity. First, an ROI approach using one-way ANOVA tested whether activation differed by group in key nodes of the DMN. Combined functional/anatomical masks were created for the anterior and posterior midline regions of DMN. Specifically, a functional mask was created for deactivation during affect labeling relative to baseline across all participants. The intersection between the functional map and frontal regions in the Harvard-

Oxford Structural Atlas (Kennedy et al., 1998; Makris et al., 1999) created a combined mask for anterior DMN including mPFC. The intersection between the functional map and posterior cingulate cortex (PCC) region in the atlas created a combined mask for posterior DMN including PCC. In addition, two coordinate-based seeds were created with spherical ROIs (diameter=10mm) at the peak voxels for PCC and mPFC in a previous study of DMN (Fox et al., 2005).

Next, group-level PPI analyses were conducted to test for group differences in functional connectivity within DMN and between DMN regions and primary task-relevant regions. Specifically, two whole-brain PPI analyses were conducted – one with a PCC seed to test connectivity with other DMN regions, and one with a ventrolateral PFC seed to test connectivity between this task-relevant region and DMN. The literature-based seed was used for PCC. For ventrolateral PFC, a spherical ROI was placed at the coordinates for a peak of ventrolateral PFC activation (56, 22, 8) during affect labeling versus gender labeling among controls in prior work (Lieberman et al., 2007) in order to provide a localized seed region for ventrolateral PFC.

Medication: Secondary Analyses

In order to test for possible effects of medication, secondary analyses were conducted in which independent samples t-tests were used to compare activation in the primary regions of interest (right and left amygdala and ventrolateral PFC) for CHR participants taking medication with CHR participants not taking medication at the time of scan or within one month prior to it.

RESULTS

Demographics

Table 1 provides demographic information for the subjects. Participants consisted of 345 adolescents and young adults (216 at CHR for psychosis, 129 healthy controls). Over the course of the study, 15 of an original 217 CHR participants converted to psychosis. One converter was excluded from all analyses due to poor behavioral performance (responded to 27% of all trials), yielding a sample size of 14 converters. There were no significant differences in age ($F(2,344)=2.56$, $p=.08$) or sex ($X^2(2)=1.69$, $p=.43$) between the control, non-converter (CHR-), and converter (CHR+) groups. Current clinical status (recovery, non-recovery, or healthy control) was determined for 329 participants at follow-up (Table 2). The mean period of follow-up for the current clinical status rating was 5.3 months (S.D.=3.02; range 1-21 months). For purposes of analysis, we compared CHR cases who recovered (N=38) to CHR cases who did not recover (i.e., converted or remained symptomatic, N=162) and to controls (N=129). A total of sixteen participants did not return to the study for follow-up. There were no differences in age ($F(2,327)=2.17$, $p=.116$) or sex ($X^2(2)=0.41$, $p=.815$) between the control, non-recovery, and recovery groups.

Behavioral Performance

Accuracy

Table 3 provides details on behavioral performance for all conditions for the control, non-conversion, and conversion groups. For accuracy on responded trials, results demonstrated a main effect of condition ($F(4,338)=18.397$, $p<.0001$), a main effect of group ($F(2,338)=19.10$, $p<.0001$), and a condition-by-group interaction ($F(8,338)=3.817$, $p<.0001$) (Figure 2). Across all responded trials, converters performed with the lowest accuracy (mean=93.0%, S.D.=10.9), and non-converters' accuracy (mean=95.5%, S.D.=4.0), was intermediate between converters and

controls (mean=97.1%, S.D.=2.6). Across all participants, accuracy was highest for gender labeling and lowest for affect matching. There were no group differences on accuracy for affect labeling. For affect matching, converters performed with poorer accuracy than controls ($p<.0001$) and non-converters ($p=.003$), whereas non-converters were only distinguishable from controls at trend level ($p=.051$). For gender labeling, controls had greater accuracy than non-converters ($p=.015$) and than converters at trend level ($p=.093$). For gender matching, converters performed more poorly than non-converters ($p<.0001$) and controls ($p<.0001$), and there was a trend toward poorer accuracy among non-converters than controls ($p=.083$). For shape matching, controls performed better than non-converters ($p=.023$) and than converters at trend level ($p=.056$).

Table 4 provides details on behavioral performance for all conditions for the control, non-recovery, and recovery groups. For accuracy on responded trials, results showed a main effect of condition ($F(4,320)=17.47$, $p<.0001$) and a main effect of group ($F(2,320)=7.79$, $p<.0001$) (Figure 3). There was no significant condition-by-group interaction ($F(8,320)=1.23$, $p=.276$). Across all participants, accuracy was lowest for affect matching and highest for gender labeling. Across all responded trials, the recovery group performed with 95.44% accuracy (S.D.=5.33), which did not differ from the non-recovery group (mean=95.47%, S.D.=3.87) or the control group (mean=97.06%, S.D.=2.59). Accuracy was significantly higher for the control group than the non-recovery group ($p=.001$). CHR participants who showed symptomatic recovery did not differ from CHR participants who did not show symptomatic recovery on any of the conditions (all *p*s>.05). Controls had greater accuracy than the non-recovery group, but not compared with the recovery group, for affect matching, gender labeling, and gender matching (all *p*s>.05).

Controls performed with higher accuracy than the recovery (p=.048) and non-recovery (p=.029) groups for shape matching. There were no group differences for affect labeling.

Reaction Time

For the comparison by control, non-converter, and converter status, results demonstrated a main effect of group (F(2,342)=3.80, p=.023) and of condition (F(4,342)=180.99, p<.0001) (Figure 4) on mean RT, but the condition by group interaction was not significant (F(8,342)=1.73, p=.087). Overall mean reaction time was slower for converters than controls (p=.018) but not significantly different from non-converters (p=.130). Across all participants, RT was slowest for affect matching and fastest for shape matching.

For the comparison by control, non-recovery, and recovery status, there was a main of effect of condition (F(4,324)=383.67, p<.0001) on mean RT (Figure 5). There was no significant condition-by-group interaction (F(8,324)=1.60, p=.119) or main effect of group (F(2,324)=2.77, p=.064). CHR participants who showed symptomatic recovery did not differ from controls or CHR participants who did not show symptomatic recovery on any of the conditions (all *p*s>.05). Across all participants, RT was slowest for affect matching and fastest for shape matching.

Amygdala-Prefrontal Circuitry and Conversion to Psychosis (Aim 1)

Overview

Whole-brain analyses comparing activation by converter, non-converter, and control status supported the hypothesis of lower amygdala and ventrolateral PFC activation in converters for both emotion-processing conditions (match and label) relative to implicit baseline. To clarify whether this pattern reflects a deficit in emotion processing per se, the groups were further compared on the affect match to gender match (for the amygdala) and on the affect label to

gender label (for the ventrolateral PFC) contrasts. While the decreased activation in amygdala among converters appeared to be specific to explicit emotion processing, the decreased activation in ventrolateral PFC appeared to be related to the cognitive processes involved in discerning similarities and differences between complex stimuli and/or selection among competing alternatives. In contrast to reduced ventrolateral PFC activation, converters displayed relatively greater ACC activation, which appeared to be related to the process of matching during both explicit and implicit emotion processing. Table 5 provides details for all group differences in whole-brain activation.

Functional connectivity analyses examining differences between the conversion, non-conversion, and control groups in amygdala connectivity supported the hypothesis of altered functional connectivity among converters. However, instead of the weaker negative connectivity that was hypothesized, converters displayed positive connectivity between the amygdala and various prefrontal regions (ventrolateral PFC, inferior frontal gyrus, ACC) during affect labeling. In contrast, non-converters and controls showed negative or non-significant amygdala coupling with these regions. No group differences were observed for affect matching. The contrast of affect labeling with gender labeling suggested that differential positive amygdala-prefrontal connectivity in the conversion group was specific to labeling during explicit emotion processing. Table 6 provides details for all group differences in amygdala functional connectivity with frontal regions.

Whole-brain analyses testing for differential age-related changes in amygdala-prefrontal circuitry by converter, non-converter, and control status provided partial support for the hypothesis that converters would show altered amygdala and prefrontal activation and weaker functional connectivity with age, relative to non-converters. Converters displayed an age-related

decline in ventrolateral PFC activation for both emotion-processing conditions (match and label), as well as an age-related increase in ACC activation for affect matching, which differed from the lack of age-related change in non-converters and controls. However, age-related patterns of amygdala activation did not differ for converters and non-converters. When the affect label and gender label conditions were compared to test the specificity of these group-by-age interactions to explicit emotion processing, results suggested that converters generally display altered age-related prefrontal activation that may be associated with task complexity. Converters also displayed an age-related increase in positive amygdala-ACC functional connectivity, compared with stable connectivity in non-converters, which appeared to be characteristic of the process of labeling affective stimuli in general (regardless of whether emotion process was explicit or implicit in nature). Taken together, these findings indicate that converters exhibit altered functional connectivity and activation in the amygdala and prefrontal cortex, as well as potential abnormalities in the development of amygdala-prefrontal circuitry.

The results just summarized are presented in greater detail in the material that follows.

Functional Activation and Conversion to Psychosis

Activation in Amygdala During Emotion Processing

Relative to non-converters, converters had reduced activation in a cluster of voxels that included the right amygdala during affect matching (cluster: 15310 voxels, peak voxel: 22, -29, -6; $p<.0001$, corrected) and affect labeling (cluster: 227 voxels, peak voxel 22, -8, -17; $p=.011$, corrected), compared with implicit baseline (Figure 6). Similarly, converters showed reduced amygdala activation compared with controls for affect matching (cluster: 22482 voxels, peak voxel 24, -29, -6; $p<.0001$, corrected) and affect labeling (cluster: 575 voxels, peak voxel 24, -7, -19; $p<.0001$, corrected). The cluster for which converters had reduced activation compared with

non-converters and controls for affect matching included parahippocampal gyrus, hippocampus, thalamus, putamen, lentiform nucleus, ventrolateral PFC, inferior frontal gyrus, and insula. Non-converters did not differ from controls on amygdala or other medial temporal lobe (MTL) activation.

In order to test whether reduced amygdala activation among converters was specific to explicit emotion processing, affect matching was compared with gender matching. This contrast was selected because affect matching is generally a more robust test of amygdala activation, given that affect labeling is typically associated with lower amygdala activation than affect matching (Lieberman et al., 2007). Converters showed decreased activation in the right amygdala relative to non-converters (cluster: 228 voxels, peak voxel 34, -11, -32; p=.011, corrected) and controls (cluster: 298 voxels, peak voxel 44, -26, -25; p=.0008), which indicates that the finding of lower amygdala activation in converters may be specific to a deficit in the processing of emotional stimuli when attention is directed toward affective features of the stimuli.

Activation in Ventrolateral PFC During Emotion Processing

Compared with non-converters, converters showed reduced activation in ventrolateral PFC during affect labeling (cluster: 315 voxels, peak voxel 57, 33, 0; p=.0003, corrected) and affect matching (cluster: 15310 voxels, peak voxel: 22, -29, -6; p<.0001, corrected), relative to implicit baseline (Figure 7). Converters also displayed reduced ventrolateral PFC activation compared with controls for affect labeling (cluster: 354 voxels, peak voxel 57, 31, -1; p=.0002, corrected) and affect matching (cluster: 22482 voxels, peak voxel 24, -29, -6; p<.0001, corrected). The cluster for which converters had reduced activation compared with non-converters and controls was the same cluster identified for the amygdala, which also included

parahippocampal gyrus, hippocampus, thalamus, putamen, lentiform nucleus, inferior frontal gyrus, and insula. There were no differences in activation in ventrolateral PFC between non-converters and controls for either emotion processing condition.

To test whether reduced activation in ventrolateral PFC was specific to emotion processing, affect labeling was compared with gender labeling. This contrast was selected because prior work has suggested that affect labeling is a more robust test of ventrolateral PFC activation (e.g., Lieberman et al., 2007). For this contrast, converters did not differ from non-converters or controls, suggesting that reduced activation in this region relates more to the cognitive processes involved in processing complex affective stimuli rather than to explicit emotion processing per se. However, controls had increased bilateral ventrolateral PFC activation compared with non-converters (right cluster: 526 voxels, peak voxel 40, 6, -4; $p<.0001$, corrected; right cluster: 212 voxels, peak voxel -36, 14, 1; $p=.02$, corrected), which suggests that differentially lower ventrolateral PFC activation during emotion labeling is a marker of vulnerability rather than a specific predictor of psychosis. To test whether reduced activation in ventrolateral PFC was specific to labeling processes, the affect labeling condition was compared with affect matching. There were no group differences, suggesting that lower ventrolateral PFC activation in converters is associated with processing complex stimuli generally and not specific to labeling or matching processes per se.

Activation in ACC During Emotion Processing

Converters showed relatively greater activation in ACC (BA 32), compared with non-converters and controls for affect matching (cluster: 1160 voxels, peak voxel 18, 37, -5; $p<.0001$, corrected) (Figure 8). The difference in activation manifested as a greater deactivation in ACC for affect matching compared with baseline in the non-converter and control groups. There were

no group differences for affect labeling, as converters showed a comparable level of deactivation when affect labeling was compared with implicit baseline. To test whether the relatively increased ACC activation in converters was specific to affect matching, the groups were compared on ACC activation for affect matching relative to gender matching. The group difference in ACC activation was significant (cluster: 215 voxels, peak voxel -14, 55, 22; p=.018, corrected), such that converters showed a deactivation in ACC from gender matching to affect matching (relative to no difference between the conditions for non-converters and controls). These results suggest that converters may display greater ACC activation (or less of a deactivation) than non-converters for the process of matching affective stimuli, regardless of whether emotion processing is explicit or implicit in nature.

Functional Connectivity and Conversion to Psychosis

Functional connectivity analyses demonstrated that converters had positive coupling between the amygdala and prefrontal regions, whereas non-converters and controls displayed negative or non-significant coupling in this circuitry. For affect labeling (relative to implicit baseline), converters exhibited positive functional connectivity between the right amygdala and ventrolateral PFC, whereas non-converters showed no significant connectivity and controls showed negative amygdala-ventrolateral PFC (cluster: 229 voxels, peak voxel -53, 23, -1; p<.0001, corrected) (Figure 9). In addition, converters displayed positive functional connectivity between the amygdala and a cluster including inferior frontal gyrus and middle frontal gyrus, compared with negative connectivity in non-converters and no connectivity with these regions in controls (cluster: 156 voxels, peak voxel -38, 47, 11; p=.001, corrected) (Figure 10). Results of PPI analyses conducted with the left amygdala seed produced similar findings, such that converters uniquely displayed positive functional connectivity between the left amygdala and

ventrolateral PFC and inferior frontal gyrus. In addition, converters displayed differential positive connectivity between the left amygdala and ACC, whereas non-converters displayed negative amygdala-ACC connectivity (Figure 11; cluster: 106 voxels, peak voxel -24, 57, 14; p=.021, corrected). No group differences were observed for affect matching, consistent with prior evidence that amygdala-prefrontal functional connectivity is best probed using the affect labeling condition (Lieberman et al., 2007; Fakra et al., 2008).

To test whether these differences in amygdala-prefrontal functional connectivity were specific to the condition of affect labeling, groups were compared on affect labeling versus gender labeling. Similar to the findings relative to baseline, converters displayed stronger positive functional connectivity between the amygdala and prefrontal regions than non-converters. Specifically, converters had positive functional connectivity between the amygdala and a cluster of regions including ventrolateral PFC, inferior frontal gyrus, and insula, compared with non-converters who did not display significant connectivity (cluster: 319 voxels, peak voxel 26, 27, 1; p<.0001, corrected). In addition, converters showed positive functional connectivity between the amygdala and ACC, relative to negative amygdala-ACC functional connectivity observed in non-converters (cluster: 201 voxels, peak voxel -14, 55, 5; p=.0001). Given that no group differences were observed for affect matching and that the group differences held when affect labeling was compared with gender labeling, results suggest that that differential positive connectivity in converters is specific to affect labeling. Group differences in amygdala functional connectivity were significant over and above the effect of amygdala activation for affect labeling.

Age-Related Differences in Amygdala-Prefrontal Circuitry associated with Conversion

Conversion and Age-Related Prefrontal Activation

Compared with a lack of age-related change in non-converters, converters showed a decrease in age-related activation in ventrolateral PFC (BA 47, 45) during affect matching (cluster: 1020 voxels, peak voxel 51, 16, 1; p<.0001, corrected) and affect labeling (cluster: 552, peak voxel 22, 18, -23; p<.0001, corrected) (Figure 12). In addition, the age-related decrease in activation was significant in converters compared to controls for affect matching (cluster: 1031 voxels, peak voxel 51, 16, 1; p<.0001, corrected) and affect labeling (cluster: 387 voxels, peak 22, 18, -23, p<.0001, corrected).

Differences in age-related ACC activation were also observed in the conversion group. Specifically, converters displayed increased ACC activation with age for affect matching, whereas non-converters and controls did not show age-related change in the ACC (cluster: 366 voxels, peak voxel -2, 27, -1; p<.0001, corrected). However, converters did not differ from non-converters for affect labeling.

To test whether age-related changes in prefrontal activation were specific to emotion processing, the groups were compared on affect labeling versus gender labeling and on affect matching versus gender matching. There were no group-by-age interactions identified for these higher-order contrasts, suggesting that converters may display differential age-related prefrontal activation when processing complex affective stimuli, but not specifically to explicit emotion processing.

Conversion and Age-Related Amygdala-Prefrontal Functional Connectivity

Compared with stable functional connectivity in non-converters and controls, converters displayed an age-related increase in positive amygdala-ACC functional connectivity for affect labeling (relative to implicit baseline; cluster: 663 voxels, peak voxel -8, 52, -4; p<.0001, corrected) (Figure 13). The cluster extended from bilateral ACC (BA 32) to bilateral medial

frontal gyrus (BA 10). This finding was replicated in the PPI analysis with the left amygdala seed (cluster: 596 voxels, peak voxel -2, 58, 3; $p<.0001$, corrected). No group-by-age interactions were observed for amygdala functional connectivity during affect matching. To test whether the differential age-related pattern in converters was specific to affect labeling, age-related functional connectivity was compared for affect labeling versus gender labeling. There were no group differences in age-related functional connectivity, suggesting that relatively greater age-related positive amygdala-ACC connectivity in converters may be characteristic of the process of labeling complex stimuli in general, but not specific to explicit emotion processing.

Amygdala-Prefrontal Circuitry and Time to Conversion

To elucidate the relationship between amygdala-prefrontal circuitry and conversion, analyses tested whether amygdala activation, ventrolateral PFC activation, or amygdala-ventrolateral PFC functional connectivity predicted time to conversion. Because converters displayed reduced activation in the amygdala and ventrolateral PFC during both emotion-processing conditions (match and label), mean percent signal change in the clusters for significant group differences were averaged across these two conditions. Ventrolateral PFC activation (averaged across affect labeling and affect matching, relative to implicit baseline) predicted time to conversion, over and above age, sex, and percent of responded trials ($F(8)=11.76$, $p=.027$). Specifically, within the conversion group, lower ventrolateral PFC activation at baseline was associated with a shorter time to the onset of psychosis (Figure 14).

Amygdala activation and amygdala-prefrontal functional connectivity did not predict time to conversion.

Amygdala-Prefrontal Circuitry and Recovery from the CHR State (Aim 2)

Overview

Whole-brain maps of activation by recovery, non-recovery, and control status supported the hypothesis that CHR participants who subsequently recovered symptomatically from the prodromal syndrome would exhibit amygdala-prefrontal circuitry that was different from those who did not recover but would resemble circuitry in healthy controls. Specifically, amygdala activation in the recovery group was higher than in the non-recovery group, but did not differ from the control group, for affect matching. The hypothesis was not supported for affect labeling, as there were no group differences in amygdala activation for affect labeling. When affect matching and gender matching were compared to clarify the specificity of the effect, the recovery group consistently displayed relatively greater amygdala activation. Thus, increased amygdala activation in the recovery group appears to be specific to matching during explicit emotion processing.

Comparing prefrontal activation by recovery, non-recovery, and control status partially supported the hypothesis of prefrontal activation in the recovery group that differed from the non-recovery group but not from controls. Specifically, relative to the non-recovery group, the recovery group showed increased activation in ventrolateral PFC for both emotion-processing conditions and increased activation in ACC for affect labeling. However, ventrolateral PFC activation and ACC activation in the recovery group were also higher than in controls for affect labeling (but not for affect matching). To clarify the nature of this particularly elevated pattern of prefrontal activation among CHR participants who recovered, the groups were compared on affect labeling relative to gender labeling. Results suggested that the recovery group exhibits elevated ventrolateral PFC activation in general compared with the non-recovery group, but also

ventrolateral PFC activation that is greater than in controls for the process of labeling. Similarly, ACC activation appeared to be greater than both the non-recovery and recovery groups for the general process of labeling. Whole-brain group differences in activation are detailed in Table 7.

Functional connectivity analyses that tested for differences between the recovery, non-recovery, and control groups supported the hypothesis that the recovery group would display amygdala-prefrontal functional connectivity that differed from the non-recovery group but was similar to amygdala coupling in controls. In particular, CHR participants who subsequently recovered showed stronger negative functional connectivity between the right amygdala and prefrontal regions (ventrolateral PFC, subgenual ACC) than the non-recovery group, who displayed non-significant amygdala-prefrontal connectivity, for affect labeling. The pattern of negative amygdala-prefrontal coupling in the recovery group was consistent with negative coupling observed among controls in the present sample and in prior studies of healthy adults. Though findings were generally similar for left amygdala connectivity, the recovery group also displayed positive connectivity between the left amygdala and ACC for affect labeling, whereas the non-recovery group did not show significant connectivity with ACC. To test whether the finding of differential functional connectivity between the recovery and non-recovery groups was specific to labeling during explicit emotion processing, the groups were compared on affect labeling relative to gender labeling. While negative amygdala connectivity with ventrolateral PFC and subgenual ACC was indeed specific to affect labeling, positive amygdala-ACC coupling appeared to be characteristic of the process of labeling in general. Table 8 provides details of group differences in amygdala-prefrontal functional connectivity.

Whole-brain analyses testing for differential age-related changes in activation by recovery, non-recovery, and control status did not fully support the hypothesis that the recovery

group would show age-related patterns of amygdala-prefrontal activation and functional connectivity that differed from the non-recovery group but not from controls. The recovery group displayed an age-related increase in ACC activation, which differed from the non-recovery group but not from controls, for affect labeling. However, age-related patterns of amygdala activation did not differ between the recovery and non-recovery groups. Because there were no group-by-age interactions for affect matching or when affect labeling was compared with gender labeling, the age-related change in ACC activation in the recovery group may be specific to the process of labeling affective stimuli, regardless of whether attention is directed toward the affective features of the stimuli. Compared with stable functional connectivity in the non-recovery and control groups, the recovery group displayed an age-related increase in positive functional connectivity between the amygdala with ACC and medial frontal gyrus during affect labeling. Age-related patterns of functional connectivity for affect matching did not differ by group. There were no group differences in age-related functional connectivity for affect labeling relative to gender labeling, suggesting that relatively greater age-related positive amygdala connectivity with ACC and medial frontal gyrus in the recovery group may be characteristic of labeling in general. Taken together, amygdala-prefrontal circuitry in the recovery group was marked by several features (e.g., amygdala activation, amygdala-ventrolateral PFC functional connectivity) that differed from the non-recovery group but not from controls. However, other aspects of the circuitry, such as relatively greater ventrolateral PFC activation and age-related changes, also differed from amygdala-prefrontal circuitry in healthy controls.

The findings just summarized are presented in greater detail in the material that follows.

Functional Activation and Recovery

Activation in Amygdala During Emotion Processing

Relative to the non-recovery group, the recovery group had higher activation for affect matching (relative to implicit baseline) in a cluster of voxels including the right amygdala (but also parahippocampal gyrus, insula, inferior frontal gyrus (BA 44), and superior temporal gyrus; cluster: 2315 voxels, peak voxel 36, 1, 17; $p<.0001$, corrected) (Figure 15). However, the recovery group did not display differential amygdala activation for affect labeling. Compared with the non-recovery group, controls also displayed increased activation in the right amygdala and parahippocampal gyrus (cluster: 386 voxels; peak 16, -5, -17; $p<.0001$, corrected) for affect matching but not affect labeling. The recovery and control groups did not differ on amygdala activation.

To test whether heightened amygdala activation in the recovery group was specific to explicit emotion processing, we compared affect matching with gender matching. The recovery group exhibited greater activation than the non-recovery group in a cluster comprising right amygdala and parahippocampal gyrus (cluster: 410 voxels, peak 10, -16, -18; $p<.0001$, corrected), which suggests that increased amygdala activation in the recovery group may be specific to emotion processing (when attention is directed toward the affective features of stimuli). Healthy controls also showed heightened right amygdala and parahippocampal gyrus activation compared with the non-recovery group (cluster: 284 voxels, peak voxel 22, 1, -29; $p=.001$) but did not differ from the recovery group.

Activation in Ventrolateral PFC During Emotion Processing

Consistent with the hypothesis for prefrontal activation, compared with the non-recovery group, the recovery group displayed increased activation in ventrolateral PFC for affect labeling in the right ventrolateral PFC (cluster: 953 voxels, peak voxel 46, 27, -10; $p<.0001$, corrected) and affect matching (cluster: 288 voxels, peak voxel -34, 25, -1; $p=.0009$, corrected) (Figure 16).

Controls also showed greater ventrolateral PFC activation than the non-recovery group for affect labeling (cluster: 350 voxels, peak voxel 34, 37, 6; p=.0002, corrected) and affect matching (cluster: 395 voxels, peak voxel -34, 20, 18; p<.0001; also included insula). For affect labeling but not matching, the recovery group showed greater activation in prefrontal regions than the control group in a cluster of voxels extending between ventrolateral PFC and ACC (cluster: 3160 voxels, peak voxel -16, 61, 10), p<.0001, corrected).

To test whether higher ventrolateral PFC activation in the recovery group was specific to emotion processing, affect labeling was contrasted with gender labeling. There were no differences, suggesting that CHR participants who recovered may show increased activation in ventrolateral PFC related to processing complex affective stimuli rather than to explicit emotion processing per se. Affect labeling was compared with affect matching to test the specificity of elevated ventrolateral PFC to affect labeling, given that it is considered a more robust test of prefrontal activation than matching. The recovery group displayed increased activation in right ventrolateral PFC (BA 47) relative to controls (cluster: 218 voxels, peak voxel 38, 32, -12, p=.017, corrected), but not relative to the non-recovery group (the group difference was subthreshold). These results are consistent with the finding that the recovery group showed atypically elevated ventrolateral PFC activation (relative to controls) during affect labeling but not matching, when compared with implicit baseline. Given that the recovery group displayed increased ventrolateral PFC activation relative to the control group for affect labeling relative to implicit baseline and to affect matching, but not when compared to gender labeling, findings suggest that the recovery group may be characterized by atypically enhanced ventrolateral PFC activation to labeling in general.

Activation in ACC During Emotion Processing

Group differences also existed for activation in ACC, such that the recovery group showed relatively greater activation in regions of ACC (BA 32, BA 24) for affect labeling, relative to the non-recovery and control groups (cluster: 1805 voxels, peak voxel 32, 0, 39; $p<.0001$, corrected) (Figure 17). In particular, the recovery group showed less of a deactivation than the non-recovery and control groups when affect labeling was compared with implicit baseline. There were no group differences for affect matching, during which all groups deactivated ACC to a similar extent. To test whether greater activation in the recovery group was specific to the labeling of affective stimuli during explicit emotion processing (i.e., affect labeling), activation for each group was compared for affect labeling versus gender labeling. Given that there was no difference for this higher-order contrast, the results suggest that the recovery group may display greater ACC activation during the process of labeling affective stimuli, regardless of whether attention is directed to affective features of the stimuli.

Functional Connectivity and Recovery

Functional connectivity analyses demonstrated that CHR participants who subsequently recovered showed amygdala-prefrontal coupling that resembled connectivity in controls but was different from the non-recovery group. For affect labeling (relative to implicit baseline), the recovery and control groups displayed negative functional connectivity between the right amygdala and ventrolateral PFC, whereas the non-recovery group displayed non-significant amygdala-ventrolateral PFC coupling (cluster: 242 voxels, peak voxel 51, 36, -10; $p<.0001$, corrected) (Figure 18). The recovery group also had negative amygdala connectivity with subgenual ACC (BA 25), whereas the non-recovery group did not have significant amygdala-subgenual ACC coupling (cluster: 172 voxels, peak voxel 4, 4, -7; $p=.0002$, corrected) (Figure 19). While the cluster was focused on subgenual ACC, it also included putamen and caudate. PPI

analyses with the left amygdala seed demonstrated similar group differences for the ventrolateral PFC, as the recovery group showed stronger negative amygdala-ventrolateral PFC coupling than the non-recovery group (cluster: 132 voxels, peak voxel 51, 36, -10; p=.0033). For the left amygdala, group differences were also observed for functional connectivity with the ACC. Whereas controls showed negative amygdala-ACC functional connectivity and the non-recovery group did not display significant coupling between these regions, the recovery group displayed positive amygdala-ACC functional connectivity (cluster: 229 voxels, peak voxel 2, 50, -11; p<.0001, corrected) (Figure 20).

There were no significant group differences for affect matching, consistent with previously reported specificity of amygdala-ventrolateral PFC functional connectivity to affect labeling (e.g., Lieberman et al., 2007; Fakra et al., 2008). To test whether the finding of differential functional connectivity between the recovery and non-recovery groups was specific to affect labeling, the groups were compared on affect labeling relative to gender labeling. Similar group differences emerged, such that the recovery group demonstrated negative functional connectivity between the amygdala and ventrolateral PFC compared with positive connectivity in the non-recovery group (cluster: 288 voxels, peak voxel 53, 33, 4; p<.0001, corrected). The same pattern of functional connectivity was observed for amygdala-subgenual ACC coupling (cluster: 187 voxels, peak voxel 16, 9, -9; p=.0001, corrected). These results suggest that the finding of stronger negative functional connectivity in the recovery group is specific to the process of labeling during explicit emotion processing. However, the group difference in amygdala-ACC functional connectivity was not observed for the contrast of affect labeling with gender labeling, indicating that stronger positive amygdala-ACC coupling in the recovery group may characterize the process of labeling affective stimuli in general, regardless

of whether attention is specifically directed to affective features. Group differences in amygdala functional connectivity were significant over and above the effect of amygdala activation for affect labeling.

Age-Related Differences in Amygdala-Prefrontal Circuitry associated with Recovery

Recovery and Age-Related Prefrontal Activation

The recovery group showed increased ACC activation with age in bilateral ACC (BA 32, 24), whereas the non-recovery group decreased in activation with age (cluster: 205 voxels, peak voxel -8, 51, 22; p=.027, corrected) (Figure 21). There was no age-related difference in ACC activation between controls and the recovery or non-recovery group. The altered age-related pattern of prefrontal activation identified in the recovery group may be specific to the process of labeling, as no group-by-age interactions were identified for affect matching (versus implicit baseline), or when affect labeling was compared with gender labeling.

Recovery and Age-Related Amygdala-Prefrontal Functional Connectivity

Compared with stable functional connectivity in the non-recovery and control groups, the recovery group displayed an age-related increase in positive amygdala-ACC functional connectivity during affect labeling (relative to implicit baseline; cluster: 153 voxels, peak voxel -4, 40, 20; p=.0013, corrected) (Figure 22). In addition, the recovery group showed an increase in functional connectivity between the right amygdala and medial frontal gyrus (BA 10) with age, relative to a lack of age-related change in the non-recovery and control groups (cluster: 429 voxels, peak voxel 4, 54, -4; p<.0001, corrected). Age-related patterns of functional connectivity for affect matching did not differ by group. To test whether the differential age-related pattern of amygdala-prefrontal functional connectivity in the recovery group was specific to affect labeling, affect labeling was compared with gender labeling. There were no group differences in age-

related functional connectivity, suggesting that relatively greater age-related positive amygdala connectivity with ACC and medial frontal gyrus in the recovery group may be characteristic of labeling in general.

Task-Related Circuitry among Controls and CHR Group

Validation of Expected Pattern of Functional Connectivity Within Controls

Within-group analyses of activation and functional connectivity were conducted to facilitate interpretation of the differences between groups and conditions. Similar to prior studies of healthy adults, the present sample of controls showed negative functional connectivity between the amygdala and prefrontal regions during emotion processing. Specifically, controls displayed negative functional connectivity between the amygdala and a cluster of voxels including ventrolateral PFC during affect labeling (relative to implicit baseline) (cluster: 1347 voxels, peak voxel -53, 25, -3, $p<.0001$, corrected). In addition, controls exhibited negative amygdala-ACC functional connectivity during affect labeling (cluster: 563 voxels, peak voxel -12, 54, 27; $p<.0001$, corrected).

Amygdala Activation During Emotion Processing

Analyses of amygdala activation within the control and CHR subgroups revealed important differences in activation to each condition (Figure 23). Results of a between-subjects repeated measures ANOVA of amygdala activation (using the anatomically defined right amygdala mask) showed a main effect of condition ($F(4,343)=4.447$, $p=.001$) and a condition by group (control, CHR) interaction ($F(4,343)=3.071$, $p=.016$). Within controls, amygdala activation was highest for affect matching. However, while the control group displayed the expected pattern of amygdala-prefrontal connectivity and increased amygdala activation to affect

matching relative to affect labeling, controls also displayed relatively lower amygdala activation to gender labeling, gender matching, and shape matching.

In contrast to the pattern of amygdala activation during emotion processing in controls, CHR participants showed a trend toward reduced amygdala activation to affect matching than affect labeling ($t(215)=1.79$, $p=.075$), suggesting that they did not experience the same differential effect of labeling on amygdala activation. In addition, the conversion group did not display greater amygdala activation for affect matching compared with affect labeling. In addition, it was observed that the recovery group displayed heightened amygdala activation during both affective conditions but also during gender labeling. Due to differences in activation to the non-emotional control conditions among the CHR groups, activation was compared with implicit baseline to minimize differences in the baseline condition used for fMRI contrasts in analyses of group comparisons.

Default Mode Network: Secondary Analyses

Analyses testing for possible effects of DMN on the primary results revealed no group differences in DMN activation or functional connectivity. Specifically, one-way ANOVAs revealed that activation in relevant DMN nodes did not differ between the conversion, non-conversion, recovery, non-recovery, or control groups (all ps > .05). In addition, the whole-brain PPI analyses revealed that there were no group differences in PCC seed-based connectivity with other DMN regions, ventrolateral PFC, or amygdala. There were also no group differences in ventrolateral PFC seed-based connectivity with regions of DMN.

Medications: Secondary Analyses

Of 216 CHR participants, 101 (46.7%) were currently taking medication (including antipsychotics, antidepressants, anticonvulsants, stimulants, and lithium) at the time of the MRI scan or within one month prior to it (6 of 14 (42.9%) converters; 95 of 202 (47.0%) non-converters). Independent samples t-tests did not show any differences in brain activation in left and right ventrolateral PFC or left and right amygdala for affect labeling and affect matching (versus implicit baseline) for medicated versus unmedicated participants (all *p*s >.05), with the exception that medicated participants had increased activation in the left amygdala during affect labeling (t(214)=2.203, p=.029). In addition, medicated and unmedicated participants did not differ on amygdala-ventrolateral PFC functional connectivity or amygdala-ACC functional connectivity (*p*s >.05). Analyses that specifically compared CHR participants taking antipsychotic medications (n=53) versus CHR participants who were unmedicated or taking a non-antipsychotic medication (n=163) showed no differences in ventrolateral PFC or amygdala activation during affect labeling or affect matching (relative to implicit baseline) (all *p*s>.05). Similarly, there were no differences between CHR participants who were either taking (n=55) or not taking (n=161) antidepressant medication, or between CHR participants who were either taking (n=30) or not taking (n=186) lithium or anticonvulsants. CHR participants taking stimulant medication (n=34) showed greater amygdala activation in the left amygdala to affect labeling (relative to implicit baseline) than participants not taking stimulants (n=182) (t(214)=2.43, p=.016).

DISCUSSION

The present study investigated whether neural abnormalities related to emotion processing predate the onset of psychosis and examined how alterations in amygdala-prefrontal

circuitry may predict clinical outcomes among adolescents and young adults at CHR for psychosis. Findings revealed differential activation and functional connectivity in amygdala-prefrontal circuitry at baseline among CHR participants who later converted to psychosis or recovered symptomatically from the high-risk syndrome. Specifically, compared with non-converters and healthy controls, converters exhibited reduced activation in the amygdala and ventrolateral PFC, but increased activation in other distributed regions, during emotion processing. In addition, converters showed positive amygdala-prefrontal functional connectivity, compared with the expected pattern of negative functional connectivity in this regulatory circuit. The recovery group displayed amygdala-prefrontal function that generally resembled circuitry in controls but that differed from the non-recovery group. Specifically, the recovery group showed increased amygdala and ventrolateral PFC activation, as well as stronger inverse amygdala-prefrontal functional connectivity, compared with the non-recovery group. The present findings suggest that the extent to which amygdala-prefrontal circuitry is abnormal or typical among individuals at risk for psychosis may predict the severity of clinical course. Taken together, these results provide novel insight into the nature of emotion processing deficits in the development of psychosis and may enhance early identification of risk for psychosis.

Conversion to Psychosis and Amygdala-Prefrontal Circuitry

At-risk participants who later converted to psychosis exhibited notable alterations in brain activation and functional connectivity as early as one year prior to the onset of psychosis. Converters displayed reduced activation in the amygdala and ventrolateral PFC, primary regions involved in the emotion processing task (e.g., Lieberman et al., 2007), compared with non-converters and controls. Converters also displayed altered function in the ACC (medial frontal

cortex), a region that is thought to mediate interactions between the amygdala and ventrolateral PFC, which manifested as less of a deactivation in ACC during affect matching relative to baseline. Moreover, prefrontal activation within the conversion group demonstrated functional significance in predicting when CHR participants experienced the onset of psychosis. Specifically, ventrolateral PFC activation averaged across affect labeling and matching was positively associated with time to conversion, such that CHR participants with lower prefrontal activation were more likely to convert earlier than those with higher prefrontal activation. Of note, the ventrolateral region of PFC in which activation was low and predictive of conversion in the present sample overlaps with the prefrontal region identified in prior studies of structural gray matter loss in psychotic disorders (Pantelis et al., 2003; Sun et al., 2009). Thus, it may be that progressive decreases in gray matter volume relate to the functional deficits in PFC among at-risk individuals who develop psychosis.

Findings of reduced activation in the amygdala and prefrontal cortex, key nodes of the distributed network of brain regions involved in emotion processing (Adolphs et al., 1994; Banks et al., 2007; M. J. Kim et al., 2011; Kober et al., 2008; Ochsner et al., 2002; Phan, Wager, Taylor, & Liberzon, 2002), are consistent with prior studies that have demonstrated decreased activation in emotion-related regions in patients with schizophrenia. In particular, reduced amygdala activation in schizophrenia has been observed across various tasks (Gur et al., 2002, 2007; Hempel et al., 2003; Kosaka et al., 2002; Phillips et al., 1999; Taylor et al., 2005; Williams et al., 2004, 2007) and highlighted as a region of consistent abnormality in meta-analyses (Li et al., 2010; Anticevic et al., 2010; Taylor et al., 2012). When examining neuroimaging studies of emotion perception, a recent meta-analysis identified a region focused on the amygdala as the area with the highest density of findings for the contrast of healthy controls versus patients with

schizophrenia (Taylor et al., 2012). The present observation of reduced amygdala activation in converters fits with the direction of this meta-analytic result and the nature of the task (e.g., affect labeling as emotion perception). While the meta-analysis observed more consistent amygdala hypoactivation during implicit processing, they also identified a cluster in the right amygdala that showed reduced activation in patients across studies of explicit emotion processing. The laterality of this finding is consistent with the right-lateralized group differences for the amygdala in the present study. In addition, Taylor and colleagues (2012) found that hypoactivation in the amygdala was observed in patients with schizophrenia even after controlling for task difficulty and complexity. Similarly, we observed reduced amygdala activation in converters compared with non-converters for affect labeling, when performance differences were minimized. Some research (e.g., Anticevic et al., 2012) has emphasized that patients with schizophrenia may fail to display "specific reactivity" of the amygdala, based on the observation of group differences only when negatively valenced stimuli are contrasted with neutral stimuli. However, other studies have observed no differences in amygdala activation for the contrast of emotional with neutral stimuli (Anticevic, Repovs, et al., 2012; Holt et al., 2006). In the present study, converters displayed reduced amygdala activation despite contrasts that were matched on valence (e.g., affect match compared with gender match). Thus, it may be that patients who later develop psychosis more generally display reduced amygdala activation when asked to process and make explicit decisions about complex affective stimuli or select between competing alternatives.

In addition to reduced activation in the amygdala, converters demonstrated reduced activation in distributed regions. For both emotion-processing conditions, converters showed less activation than non-converters in inferior frontal gyrus (BA 9) parahippocampal gyrus, putamen,

lentiform nucleus, and inferior and middle occipital gyrus. Lower activation for converters in subgenual ACC (BA 25), postcentral gyrus, inferior parietal lobe, and cerebellum was observed only for affect labeling. Reduced activation for converters in hippocampus, thalamus, insula, superior parietal lobe, precuneus, superior frontal gyrus, precentral gyrus, and cingulate gyrus was observed only for affect matching. The areas of lower activation in converters in the present study are consistent with findings of decreased activation in medial frontal cortex and subcortical structures such as the thalamus in a recent meta-analysis (Taylor et al., 2012). Similarly, prior research on patients with schizophrenia using the same affect labeling and matching task has demonstrated reduced activation in the amygdala, inferior frontal gyrus, putamen, superior temporal cortex, and hypothalamus during affect matching (Fakra et al., 2008), consistent with the regions of reduced activation observed in the present sample of converters.

However, it is important to note that the conversion group displayed greater activation than the non-conversion and control groups in various regions, suggesting that the observed impairment in emotion processing is not confined to underactivation. Specifically, converters exhibited increased activation in cuneus and fusiform gyrus during both affect labeling and affect matching. Of note, cuneus and fusiform gyrus were also identified as regions of greater activation in patients with schizophrenia in a recent meta-analysis (Taylor et al., 2012). For patients with schizophrenia, the cuneus was specifically greater in activation for studies of emotion perception, whereas the fusiform gyrus was also more activated in studies that controlled for difficulty level. However, findings of reduced fusiform gyrus activation during emotion processing in schizophrenia have also been reported (Fakra et al., 2008; Li et al., 2010; Quintana, Wong, Ortiz-Portillo, Marder, & Mazziotta, 2003). Though the fusiform gyrus is central to face processing, the cuneus is less associated with emotion processing (e.g., Kober et

al., 2008). In the present study, converters also displayed increased activation in superior temporal gyrus, insula and caudate during affect matching, and in posterior cingulate, precuneus, and superior/middle frontal gyrus during affect labeling. Some of these regions such as precuneus and superior frontal gyrus were also observed to be hyperactive in patients with schizophrenia performing the same task (Fakra et al., 2008). Thus, while the nature of increased activation in the conversion group is unclear, it may be that converters use different circuitry to process emotions or that the recruitment of additional regions is associated with compensatory processing. In line with the possibility of compensatory processing or a less effective network for processing emotions, the conversion group displayed poorer accuracy than the non-conversion and control groups for affect matching. However, there were no differences in accuracy for affect labeling.

In order to elucidate the nature of interactions between the amygdala and cortical regions prior to the onset of psychosis, functional connectivity analyses were conducted in the present study. By contrast to the general pattern of negative amygdala-prefrontal functional connectivity observed for the control and non-conversion groups, the conversion group exhibited *positive* functional connectivity between the amygdala and prefrontal regions such as ventrolateral PFC and ACC. Given the consistent observation of negative functional connectivity between the amygdala and PFC in healthy adolescents and adults in the present sample and prior task-based studies (Hare et al., 2008; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; H. Kim et al., 2003; Kim et al., 2011; Lieberman et al., 2007), this pattern of positive connectivity may not represent a basic difference in strength of functional connectivity, but likely a qualitatively different nature of the relationship between the amygdala and PFC prior to the onset of psychosis. Although fMRI methodology cannot determine the nature of inhibitory or excitatory

influences, negative amygdala-PFC functional coupling has been theorized to reflect top-down prefrontal regulation of amygdala activity (Hariri et al., 2003; Kim et al., 2003; Hare et al., 2008; Lieberman et al., 2007; Fakra et al., 2008). Thus, it may be that the nature of amygdala-prefrontal interaction is characterized by upregulation in converters, instead of downregulation that is typically observed during emotion regulation in healthy adults.

Moreover, the finding of weaker negative, or non-significant, amygdala-prefrontal functional connectivity in adult patients with schizophrenia (e.g., Fakra et al., 2008) suggests that functional connectivity might change with development or symptom progression in individuals who convert to psychosis. For example, it may be that individuals at elevated risk or in the process of developing psychosis initially display positive functional connectivity that subsequently changes to disconnectivity or weak negative connectivity. Though highly exploratory at present, this idea would be consistent with the strong evidence for a neurodevelopmental model of schizophrenia that posits abnormalities in brain development (e.g., excessive or accelerated synaptic pruning, progressive gray matter loss) as contributing to the onset of psychosis (Karlsgodt et al., 2008; McGlashan & Hoffman, 2000). Though the present study may have lacked sufficient power to adequately test for differential developmental patterns of functional connectivity in the conversion group, it is notable that recent developmental research indicates that a shift from positive to negative functional connectivity occurs during the transition to adolescence in the typical development of amygdala-prefrontal circuitry (Gee et al., 2013). As such, a hypothesis that stems from the current study is that conversion to psychosis may be associated with delayed or altered development of the mature phenotype of amygdala-prefrontal functional connectivity.

Recovery from the CHR State and Amygdala-Prefrontal Circuitry

The primary goal of the second aim in the current study was to test the model that less severe deficits among CHR participants would be associated with a better clinical course. Consistent with the prediction that improved outcomes would be associated with more typical activation and functional connectivity, CHR participants who symptomatically recovered from the at-risk state displayed amygdala-prefrontal circuitry that more closely resembled that of healthy controls. In addition, the recovery group did not differ behaviorally from controls. During emotion processing, the recovery group showed amygdala activation that was increased compared with the non-recovery group but indistinguishable from the control group during affect labeling and matching. The finding of relatively greater amygdala activation among participants who recover over the next six months may be consistent with prior evidence that altered amygdala activation is more related to clinical state than genetic risk (Rasetti et al., 2009). In addition, the recovery group displayed heightened activation in ventrolateral PFC and ACC, relative to the non-recovery group and also to the control group. The observation of increased activation in prefrontal regions in the recovery group relative to healthy controls may suggest prefrontal function that is particularly engaged or responsive, which may be adaptive within the context of a group that is typically characterized by gray matter loss and reduced function in prefrontal regions. It is also possible that increased activation in prefrontal regions stems from increased effort in the recovery group, which may result in the normative behavioral performance in this group. In addition to signs of typical brain activation in the recovery group, participants who recovered also demonstrated functional connectivity that resembled a typical pattern in controls. Specifically, compared with the non-recovery group, the recovery group exhibited stronger negative functional connectivity between the amygdala and ventrolateral PFC.

In addition to increased amygdala and prefrontal activation, the recovery group was characterized by greater activation across various regions during affect labeling and matching. For example, during both affect labeling and matching, the recovery group showed increased activation in superior temporal gyrus, cingulate gyrus, precuneus, and precentral gyrus than the non-recovery and control groups. In addition, the recovery group displayed increased activation in the insula and inferior frontal gyrus relative to the non-recovery and control groups during affect matching. By contrast, the recovery group did not display lower activation in any regions during affect labeling. For affect matching, the recovery group exhibited reduced activation in lingual gyrus, cuneus, superior frontal gyrus, and medial frontal gyrus, relative to the control group. Despite the general finding of increased activation in CHR participants who subsequently recover from the at-risk state, it is unclear why these individuals would display greater activation than controls. It may be that heightened activation reflects increased effort or compensatory processing to achieve a comparable behavioral outcome to controls. Though the recovery group is comprised of individuals who eventually displayed improved outcomes, it is clear by their status in the CHR group that these participants were having abnormal experiences or functioning around the time of the imaging scan. Thus, it may be that the increased activation reflects a state-like difference in individuals who otherwise show intact function in key regions for emotion processing. Moreover, the ability to recruit widespread brain regions may be adaptive and actually facilitate the process of recovery.

Amygdala Activation Within Groups

Within-group analyses revealed important ways in which the groups differed in amygdala activation to the different task conditions. In healthy adults, affect matching has been associated

with robust amygdala activation, whereas affect labeling has been uniquely associated with dampened amygdala activation via increases in ventrolateral PFC activation and negative coupling between amygdala and ventrolateral PFC (e.g., Lieberman et al., 2007). In the present study, the control group displayed higher amygdala activation for affect matching than affect labeling; however, amygdala activation was also lower (and not significantly different from affect labeling) for the conditions of gender labeling, gender matching, and shape matching. Given this pattern, it is unclear that affect labeling uniquely dampened amygdala activation through incidental emotion regulation. It may be that amygdala activation to affect matching reflects typical responsivity to emotional faces and that the other conditions result in dampened amygdala activation (e.g., through a linguistic process, cognitive load, or distraction), or it may be that the other conditions reflect basic amygdala activation to affective stimuli whereas the affect matching condition actively increases amygdala activation (e.g., through attention to perceptual features of faces). The recovery group displayed differential amygdala activation relative to the non-recovery group that was specific to matching. This finding is consistent with the idea that affect matching is a more robust test of amygdala activation. In addition, it is possible that a difference in amygdala activation was not observed for affect labeling because the recovery group experienced the expected dampening of amygdala activation via inverse amygdala-ventrolateral PFC functional connectivity during this condition. However, unlike the control group, the recovery group did not show a significant decrease in amygdala activation during affect labeling relative to affect matching.

By contrast to the specificity of the amygdala group difference to affect matching in the recovery group, converters displayed hypoactivation in the amygdala during both affect matching and affect labeling. Given differences in brain function and performance, a cautious

approach may be necessary when interpreting the nature of the task in converters. Specifically, while affect labeling has been conceptualized as a task of incidental emotion regulation in healthy controls (Lieberman et al., 2007, 2011; Tabibnia et al., 2008), it is unclear whether affect labeling serves a regulatory function in converters. Results suggested that converters experience atypically low amygdala activation; thus, there may not be sufficient reactivity to warrant regulation during the task. In addition, it is difficult to assess for regulation in the absence of heightened reactivity in the affect matching condition.

Because converters showed significantly impaired performance on affect matching but not affect labeling, it may be useful to interpret group differences in activation during affect matching in the context of differential performance and differences during affect labeling in the context of more comparable performance. Consistent with a greater deficit in performance, affect matching produced the most robust difference in amygdala activation in converters. It is unclear whether altered amygdala activation resulted in poorer performance on this condition, or it is possible that greater task difficulty may have contributed to lower amygdala activation (e.g., an effect of cognitive load). Even when the task was better matched on accuracy, converters displayed hypoactivation in the amygdala relative to non-converters. However, it is interesting to note that amygdala activation in converters did not differ from controls for affect labeling. In this way, the process of affect labeling may have served to benefit converters through relatively greater amygdala activation and accuracy.

Neurodevelopment and Clinical Outcomes

Given that disruptions in neurodevelopmental processes resulting in reduced structural and functional connectivity are hypothesized to contribute to the onset of schizophrenia

(McGlashan and Hoffman, 2000; Karlsgodt et al., 2008; Weinberger et al., 1994; Lim et al., 1999; Meyer-Lindenberg et al., 2001), the present study tested for differential patterns of age-related changes in the CHR subgroups. Findings suggest that converters display an age-related decrease in ventrolateral PFC activation for affect labeling and matching, compared with stable activation in non-converters and controls. This observation of decreased ventrolateral PFC activation in converters is consistent with prior work indicating an age-related decline in ventrolateral PFC activation among CHR participants in general (Gee et al., 2012). The conversion group also showed age-related increases in ACC activation and positive amygdala-ACC functional connectivity, relative to a lack of change in the non-conversion and control groups. Similarly, the recovery group showed increased ACC activation and amygdala-ACC functional connectivity with age. While it is unclear why participants who recover would show a similar trajectory, it may be that age-related change in ACC characterizes the at-risk state in general. Given the sample size of subgroups in the present study, the findings provide some evidence for differential development associated with clinical course; however, it is unclear to what extent these findings are robust. Future research with larger samples of CHR participants in each outcome group will be necessary for characterizing the nature of neurodevelopment in relation to clinical course.

Anterior Cingulate Cortex and Default Mode Network

Due to the important role that ACC has been shown to play in amygdala-prefrontal circuitry, such as mediating the relationship between amygdala and ventrolateral PFC during regulation (e.g., Ochsner et al., 2002; Lieberman et al., 2007), it is important to note the presence of differential ACC recruitment and connectivity in the CHR subgroups. Though less robustly

activated during the present task than ventrolateral PFC, ACC activation and connectivity were altered in both the conversion and recovery groups. ACC functional connectivity differed between the groups only for the left amygdala seed; however, examination of within-group connectivity maps suggests that this may be an issue of thresholding. For example, controls demonstrated robust negative connectivity between the right amygdala and ACC, whereas significant right amygdala-ACC functional connectivity was absent in the connectivity map for the converters. Interestingly, ACC function was altered in the same direction in both the recovery and conversion groups compared with the non-recovery and non-conversion groups, respectively. Specifically, both groups displayed positive amygdala-ACC functional connectivity (which increased in an age-related manner) and relatively greater ACC activation. Thus, it may be that these patterns of ACC function are consistent with the at-risk state but do not differentially predict clinical outcomes. In addition, it may be that altered ACC function serves a different mechanism in the recovery and conversion groups. For example, though converters showed reduced amygdala activation, positive amygdala-ACC functional connectivity may serve to upregulate amygdala reactivity in the recovery group, resulting in normalized amygdala function.

Consistent with the finding of differential ACC activation in patients with schizophrenia during both explicit and implicit emotion processing (Taylor et al., 2012), altered ACC function was observed in converters during explicit and implicit emotion processing in the present study. These findings highlight the consistent role of medial wall regions in the pathophysiology of psychosis. However, in contrast to the reduced ACC activation observed in the meta-analysis of patients with schizophrenia (Taylor et al., 2012), the present finding was of relatively greater ACC activation (i.e., less deactivation) in converters. Given the primary role of medial frontal

cortex in DMN, it is particularly difficult to interpret relative increases and decreases in the specific region of ACC identified in the current study. The interpretation of ACC function in emotion processing is compounded by prior evidence that patients with schizophrenia exhibit abnormal function in and disengagement from DMN (Whitfield-Gabrieli et al., 2009; Salgado-Pineda et al., 2011; Hasenkamp et al., 2011; Nygard et al., 2012; Guerrero-Pedraza et al., 2012). For example, a failure to deactivate DMN regions may manifest as relatively increased activation during task. This issue is further complicated by the relative nature of fMRI signal and would be greatly informed by methods such as positron emission tomography (PET) or arterial spin labeling that can measure absolute signal.

Given the relative nature of the BOLD signal in fMRI methodology and the goal to draw inferences about a special population in the present study, it is important to consider what constitutes the baseline for comparisons when interpreting the results. Because CHR participants differed in activation to the control conditions (implicit emotion processing conditions of gender labeling and gender matching, and non-emotional control of shape matching), group differences were primarily focused on contrasts of task with implicit baseline to reduce further confounds in the baseline. Examining affect labeling and affect matching relative to baseline allowed for the examination of amygdala-prefrontal circuitry during two explicit emotion-processing conditions with distinct underlying theories (e.g., incidental regulation versus potentiation of amygdala activity). Thus, affect matching tested whether CHR subgroups had the potential for increased amygdala reactivity, whereas affect labeling tested whether they displayed evidence for intact or disrupted regulatory circuitry. In addition, because behavioral performance differed for these conditions, including both allowed for a comparison of neural circuitry during different and comparable performance levels. As demonstrated in prior work (e.g., Lieberman et al., 2007), the

contrast of affect matching versus gender matching and of affect labeling versus gender labeling allowed for the isolation of the explicit affective component. However, it is important to note that the contrasts comparing two active task conditions may be less representative of these constructs in the present study due to between-group differences in activation to a given comparison task condition.

Converters in the present study exhibited reduced amygdala activation during emotion processing, suggesting the possibility of a fundamental deficit of underrecruitment of emotion-related regions. However, the relative nature of fMRI complicates the interpretation of definite hypoactivation. While fMRI studies including meta-analyses (Anticevic et al., 2012; Taylor et al., 2012; Li et al., 2010) have consistently demonstrated reduced amygdala activation in patients with schizophrenia, PET studies measuring absolute regional blood flow are less consistent. Specifically, of PET studies reporting significant differences in amygdala activation between controls and patients, two studies identified greater activation (Fernandez-Egea et al., 2010; Taylor et al., 2005) and one study observed reduced activation (Paradiso et al., 2003). Another issue related to the interpretation of amygdala hypoactivation in schizophrenia has been evidence that patients may exhibit *hyper*activation to non-significant stimuli (Hall et al., 2008). For example, one study of patients with schizophrenia demonstrated reduced activation among relevant brain regions while viewing emotional faces but hyperactivations among prefrontal and ventral midline regions during neutral faces, relative to controls (Habel et al., 2010). Though patients were able to correctly identify target emotional stimuli in this study, they judged neutral faces as more emotional than controls, specifically misinterpreting neutral faces as angry or fearful. A similar pattern of increased activation within networks relevant to emotion processing was also observed among individuals at CHR for psychosis when they viewed neutral faces

(Seiferth et al., 2008). While this remains an important issue, the design of the present study minimized potential confounds of neutral stimuli. Specifically, neutral facial stimuli were not included in the task, and all contrasts collapsed across facial expressions (which were matched across conditions).

Limitations

The CHR sample allows for a unique examination of emotion-related neural circuitry prior to the onset of overt psychosis, while minimizing common confounds such as long-term treatment with antipsychotic mediations or effects of chronic illness. The present study is limited by several factors to be addressed in future research. Despite the reduced rate of medication use in the CHR sample compared with patients with schizophrenia, approximately half of CHR participants were taking medication within one month of the MRI scan. Analyses of medication use did not suggest that it influenced the current findings. Given the multi-site nature of the study and the small sample size of converters, the present investigation may have been limited by reliability and power. Though BOLD signal is less reliable than other methods such as structural MRI, a multi-site investigation of the NAPLS study suggests that our fMRI data were reliable across sites (Gee et al., in press), particularly for activation measures. However, given the modest sample size of converters in the present study, findings may be particularly subject to type II error. With regard to analyses of conversion, it is important to note that some individuals currently classified as non-converters may still convert to psychosis. Finally, future research is warranted to elucidate group differences in DMN circuitry and how such differences may affect emotion processing. CHR subgroups in the present study displayed altered activation and connectivity with ACC, which may play an important role in the progression or recovery from

the at-risk state. However, we remain cautious in interpreting these results conclusively, given the well-documented overlap between regions in medial frontal cortex involved in DMN (e.g., Raichle et al., 2001) and emotion processing (Amodio & Frith, 2006; Lieberman, 2007; Uddin et al., 2007). Secondary analyses suggest that differences in DMN function did not account for the present findings; however, a promising line of future research may focus on the interactions between DMN function and emotion processing in schizophrenia.

Implications of the Present Study

Taken together, the present findings provide novel insight into the nature of emotion processing deficits and related alterations in neural circuitry prior to the onset of psychosis. Models of emotion-related impairment in schizophrenia indicate abnormalities in the neural circuitry subserving emotion processing, with evidence suggesting that the widespread disconnectivity observed in schizophrenia, as well as hypoactivation of central regions such as the amygdala, are likely to play a role in deficits (Aleman & Kahn, 2005; Fakra et al., 2008; Kring & Moran, 2008). However, emotion-related neural circuitry has remained less explored in at-risk patients, and much remains unknown about how emotion-processing deficits emerge prior to or during the onset of psychosis (Phillips & Seidman, 2008). The present findings of altered amygdala-prefrontal circuitry in the CHR sample provide strong evidence for the existence of abnormalities in the neural circuitry supporting emotion processing prior to the onset of overt psychosis. Moreover, these results suggest that the extent to which amygdala-prefrontal circuitry is atypical during the at-risk state predicts the severity of subsequent clinical course.

While the observations of reduced amygdala-prefrontal function in converters and enhanced prefrontal function in the recovery group lend support to the theory that hypoactivation

underlies emotion processing deficits among patients, the present findings suggest that hypoactivation is one part of a more complex issue. For example, despite reduced activation in various regions, converters demonstrated increased activation in a number of distributed regions relative to non-converters and controls. Though additional research is necessary to understand the nature of such increased recruitment, it suggests that differential recruitment, instead of general underactivation, is likely to underlie emotion-processing deficits prior to the onset of psychosis. Differences in functional connectivity observed in the present study parallel these findings in activation. Specifically, results suggest that converters may exhibit qualitatively different functional connectivity between the amygdala and prefrontal regions, in contrast to disconnectivity. While a lack of connectivity is likely to play a major role in both the onset of psychosis and emotion-related impairment, the finding of positive connectivity in converters suggests that the amygdala and prefrontal cortex are likely to show different interactions than might have been expected. In addition, these data suggest that the conversion and recovery subgroups are not two extreme ends of a continuum but may represent different classes of at-risk individuals. That is, several important findings in the present study were not a matter of degree (e.g., weaker activation or connectivity) but were instead qualitatively different (e.g., recruitment of different regions, different valence of functional connectivity).

The finding of enhanced amygdala activation in the recovery group, combined with reduced activation in the conversion group, indicates that greater amygdala reactivity or flexibility to respond may be adaptive among the high-risk group. While connectivity differed in the conversion group, we did not see evidence for disrupted prefrontal regulation leading to amygdala hyperreactivity, providing important information about the neural bases of emotion processing in schizophrenia. Unlike many psychiatric disorders in which amygdala

hyperreactivity is implicated, it may be that individuals with psychosis would benefit from increased amygdala recruitment. These results have important implications for understanding the mechanisms driving behavioral deficits in emotion processing, as well as for novel treatment approaches. While much of the research on emotion regulation has focused on top-down control of amygdala reactivity, it is also possible to upregulate amygdala activation (Ochsner et al., 2004). Moreover, evidence suggests that upregulation of emotion and amygdala reactivity relies on different regions of prefrontal cortex, as opposed to the ventrolateral region that has been identified as altered in psychosis (Pantelis et al., 2003; Sun et al., 2009) and in the at-risk state (Gee et al., 2012). Thus, patients may benefit from future research into novel mechanisms of treatment aimed at increasing amygdala reactivity or focused on regions of intact connectivity.

Consistent with the CHR paradigm, indicated prevention that is targeted toward individuals with early signs of psychosis represents a promising strategy for delaying or preventing the onset of psychosis and its debilitating effects. Crucial to this effort is the development of empirically validated criteria for identifying individuals at increased risk for psychosis. While extant prodromal criteria have greatly increased the ability to predict psychosis using approaches such as multivariate algorithms (Cannon et al., 2008; Ruhrmann et al., 2010; Yung et al., 2003), high rates of non-conversion highlight the need for the continued refinement of criteria to improve accuracy of prediction and to better inform the timing and need for intervention. Enhancing early identification will likely benefit from the integration of more quantitative, objective markers such as brain-based measures and neurocognitive performance. The present study represents a potential model for integrating biological measures, such as testing how brain function may predict time to conversion. Knowledge about the likelihood and

timing of conversion provides critical information about how to deliver psychoeducation to patients and families, provide treatment, and allocate resources.

Moreover, the current findings suggest a novel approach to research on biomarkers through the investigation of recovery. Specifically, increasing understanding of factors that contribute to recovery, as well as objective markers that predict recovery, has the potential to improve early identification and prediction of good prognosis. In addition, given potential stigma, exposure to adverse events, and limited resources for early intervention, studies of recovery from at-risk states would facilitate the identification of "false positive" cases. Despite remission from the prodrome, research suggests that the CHR state is associated with long-term disability even among non-converters (Addington et al., 2011; Schlosser et al., 2012). For example, social and role functioning in non-converters tend to remain poorer than in controls (Addington et al., 2011), and one study found that approximately half of non-converters who recovered symptomatically did not recover functionally (Schlosser et al., 2011). Thus, evidence suggests that many CHR individuals who do not convert to psychosis would likely benefit from intervention. In this way, efforts to identify individuals who will recover symptomatically could also greatly increase the ability to selectively channel these individuals into interventions that would best meet their needs.

Future Directions and Conclusions

Given the cross-sectional nature of the imaging data in the present study, longitudinal analyses will be necessary to understand how change over time in amygdala-prefrontal activation and connectivity may predict conversion to psychosis or recovery from the CHR state. Consistent with the neurodevelopmental theory of schizophrenia, the present study observed

different age-related patterns of brain function related to subsequent conversion and recovery; however, within-subject longitudinal designs will be critical to understanding how differential developmental trajectories may predict clinical outcomes. Research in this area has the potential to inform knowledge of emotion-related impairment and the design of novel interventions by elucidating the mechanisms underlying emotion-processing deficits in schizophrenia. However, this aim will depend on advanced imaging techniques that can provide the level of temporal and directional specificity needed to test the precise interactions between regions. For example, dynamic causal modeling will aid in identifying the direction of influence between regions, whereas brain-based mediation could be used to test the function of medial prefrontal regions in mediating amygdala-ventrolateral PFC connectivity. In addition, integrating resting-state fMRI and structural MRI with task-based studies of emotion processing will be critical for a stronger understanding of amygdala-prefrontal circuitry prior to the onset of psychosis. Rapidly evolving methods will help to detect specific abnormalities as well as large-scale network properties that may contribute to the onset of psychosis, but also to identify intact features of neural circuitry that could serve to facilitate strategies for intervention. As future research advances knowledge of amygdala-prefrontal function in the at-risk state, it will be critical to test specific ways in which brain-based findings can be integrated with clinically defined algorithms to enhance prediction of both clinical outcomes and socioemotional functioning.

The present investigation of amygdala-prefrontal circuitry in the CHR state produced novel insight into the nature of emotion-processing deficits and related alterations in neural circuitry related to risk for psychosis. Findings of atypical activation and functional connectivity in individuals showing early signs of risk and who later converted to psychosis provide evidence for the existence of physiological abnormalities related to emotion processing early in the

progression of psychotic illness. Moreover, the identification of specific features of amygdala-prefrontal circuitry associated with subsequent recovery from the CHR state may suggest a novel approach to brain-based markers of risk and provide knowledge that will be critical to enhancing prediction of clinical outcomes. Taken together, the current findings demonstrate that the extent to which amygdala-prefrontal circuitry is atypical during the at-risk phase predicts the course of psychotic illness. As early intervention becomes increasingly important for delaying and ultimately preventing the onset of psychosis, the current findings provide a novel approach to identifying risk and understanding the nature of emotion processing deficits to reduce functional impairment related to schizophrenia.

Table 1. Demographic Characteristics for Non-Conversion and Conversion Groups (Aim 1)

	Controls	CHR-	CHR+	F test or X^2
N	129	202	14	
Age mean (S.D.)	20.78 (4.65)	19.72 (4.34)	19.14 (3.58)	ns; F(2,344)=2.56, p=.079
Age range	12-33	13-33	14-24	
Sex	72M (55.8%)	116M (57.4%)	11M (73.3%)	ns; $X^2(2)=1.69$, p=.429
	57F (44.2%)	86F (42.6%)	4F (26.7%)	
Prodromal Criteria		178 APS (88.1%)	12 APS (85.7%)	
		12 GRD (5.9%)	1 GRD (7.1%)	
		6 YS (3.0%)	1 APS, GRD (7.1%)	
		1 BIPS (0.5%)		
		3 APS, GRD (1.5%)		
		1 APS, YS (0.5%)		
		1 APS, GRD, YS (0.5%)		
Site				
UCLA	14	25	5	
Emory	21	39	1	
Harvard	18	24	0	
Hillside	18	21	0	
UNC	22	37	4	

UCSD	8	17	1	
Calgary	11	35	2	
Yale	17	4	1	

Table 2. Demographic Information for Recovery and Non-Recovery Groups (Aim 2)

	Controls	Non-Recovery	Recovery	F test or X^2
N	129	162	38	
Age mean (S.D.)	20.78 (4.65)	19.82 (4.15)	19.39 (4.77)	ns; F(2,327)=2.17, p=.116
Age range	12-33	13-33	13-32	
Sex	72M (55.8%)	94M (58.0%)	20M (52.6%)	ns; X^2(2)=0.41, p=.815
	57F (44.2%)	68F (42.0%)	18F (47.4%)	
Site				
UCLA	14	19	8	
Emory	21	28	8	
Harvard	18	20	3	
Hillside	18	16	3	
UNC	22	35	5	
UCSD	8	13	3	
Calgary	11	26	8	
Yale	17	5	0	

Table 3. Behavioral Performance: Conversion and Non-Conversion

Behavioral Performance						
	Controls	**CHR-**	**CHR+**	**F***	**p**	**Post-hoc tests** (Tukey)**
Accuracy for Responded Trials						
Overall Responded (%)	99.05 (2.85)	98.51 (4.17)	93.93 (10.94)	9.30	p<.0001	C=CHR->CHR+
Overall Correct (% of all responded)	97.06 (2.59)	95.53 (4.03)	93.01 (5.88)	11.27	p<.0001	C>CHR+, C>CHR-, CHR->CHR+
Emotion Label	95.87 (5.13)	95.79 (5.77)	93.98 (6.65)	ns	(p=.480)	n/a
Emotion Match	94.68 (6.82)	92.51 (8.16)	84.88 (16.68)	9.50	p<.0001	C=CHR->CHR+
Gender Label	98.53 (3.00)	97.37 (3.92)	96.37 (5.11)	4.99	p=.007	C>CHR-
Gender Match	97.89 (5.68)	95.84 (8.98)	85.87 (17.82)	13.20	p<.0001	C=CHR->CHR+
Shape Match	98.11 (3.31)	96.19 (7.08)	93.93 (14.44)	4.99	p=.007	C>CHR-
Labeling	97.21 (3.13)	96.61 (3.83)	95.11 (4.24)	ns	(p=.073)	n/a
Matching	96.25 (4.45)	94.22 (6.57)	89.50 (13.15)	9.29	p<.0001	C>CHR+, C>CHR-, CHR->CHR+
Emotion	95.23 (4.43)	94.21 (5.46)	93.62 (5.73)	ns	(p=.163)	n/a
Gender	98.22 (3.46)	96.64 (5.13)	92.84 (7.50)	10.36	p<.0001	C>CHR+, C>CHR-, CHR->CHR+
Accuracy for All Trials						

Overall Correct (% of all trials)	96.10 (4.14)	94.13 (6.04)	87.64 (12.88)	14.80	p<.0001	C>CHR+, C>CHR-, CHR->CHR+
Shape Match	96.98 (4.61)	94.36 (8.79)	89.64 (17.37)	7.58	p=.001	C>CHR+=CHR-
Emotion Match	93.57 (9.21)	90.92 (10.06)	80.36 (22.40)	10.68	p<.0001	C=CHR->CHR+
Gender Match	96.71 (8.49)	94.28 (11.06)	86.43 (21.88)	6.42	p=.002	C=CHR->CHR+
Gender Label	97.83 (4.79)	96.61 (5.28)	91.43 (11.84)	9.02	p<.0001	C=CHR->CHR+
Emotion Label	95.58 (5.98)	94.65 (7.94)	91.43 (8.64)	ns	(p=.106)	n/a
Reaction Time for Responded Trials						
Overall Mean RT (ms)	1470 (272)	1533 (258)	1673 (244)	4.81	p=.009	C>CHR+
Emotion Match	1865 (386)	1927 (379)	1980 (458)	ns	(p=.275)	n/a
Emotion Label	1591 (298)	1657 (340)	1829 (367)	4.10	p=.017	C>CHR+
Gender Label	1404 (298)	1497 (311)	1684 (319)	7.25	p=.001	C>CHR+=CHR-
Gender Match	1275 (330)	1345 (325)	1418 (351)	ns	(p=.09)	n/a
Shape Match	1208 (260)	1210 (266)	1305 (288)	ns	(p=.410)	n/a

*All degrees of freedom: F(2,344)

**C=Control, CHR-=Non-Converter, CHR+=Converter

Table 4. Behavioral Performance: Recovery and Non-Recovery

Behavioral Performance						
	Controls	**Non-Recovery**	**Recovery**	**F***	**p**	**Post-hoc tests** (Tukey)**
Accuracy for Responded Trials						
Overall Responded (%)	99.05 (2.85)	98.00 (5.59)	99.03 (2.32)	ns	(p=.092)	n/a
Overall Correct (% of all responded)	97.06 (2.59)	95.47 (3.87)	95.44 (5.33)	6.88	p=.001	C>NR, C=R, R=NR
Emotion Label	95.87 (5.13)	95.57 (5.98)	96.49 (5.25)	ns	(p=.658)	n/a
Emotion Match	94.68 (6.82)	92.21 (9.12)	92.54 (8.64)	3.19	p=.043	C>NR, C=R, R=NR
Gender Label	98.53 (3.00)	97.38 (3.86)	97.74 (3.85)	3.66	p=.027	C>NR, C=R, R=NR
Gender Match	97.89 (5.68)	95.38 (9.33)	95.14 (11.09)	3.72	p=.025	C>NR, C=R, R=NR
Shape Match	98.11 (3.31)	96.10 (7.77)	95.20 (8.93)	4.52	p=.012	C>NR=R
Labeling	97.21 (3.13)	96.49 (3.94)	97.19 (3.26)	ns	(p=.205)	n/a
Matching	96.25 (4.45)	94.18 (6.82)	93.83 (8.36)	4.57	p=.011	C>NR, C=R, R=NR
Emotion	95.23 (4.43)	94.30 (5.31)	94.49 (6.03)	ns	(p=.325)	n/a
Gender	98.22 (3.46)	96.55 (496)	96.51 (6.00)	5.26	p=.006	C>NR, C=R, R=NR
Accuracy for All Trials						
Overall Correct (% of all trials)	96.10 (4.14)	93.59 (7.16)	94.54 (6.10)	6.09	p=.003	C>NR, C=R, R=NR
Shape Match	96.98 (4.61)	94.04 (9.93)	93.52 (9.71)	5.26	p=.006	C>NR, C=R, R=NR

Emotion Match	93.57 (9.21)	90.00 (12.17)	92.16 (8.78)	3.88	p=.022	C>NR, C=R, R=NR
Gender Match	96.71 (8.49)	93.64 (12.06)	94.60 (11.87)	ns	(p=.055)	n/a
Gender Label	97.83 (4.79)	96.27 (5.93)	97.03 (5.95)	ns	(p=.062)	n/a
Emotion Label	95.58 (5.98)	94.29 (8.36)	95.45 (6.81)	ns	(p=.320)	n/a
Reaction Time for Responded Trials						
Overall Mean RT (ms)	1470 (272)	1550 (260)	1495 (223)	3.26	p=.040	C>NR, C=R, R=NR
Emotion Match	1865 (386)	1947 (392)	1884 (328)	ns	(p=.195)	n/a
Emotion Label	1591 (298)	1682 (340)	1602 (306)	ns	(p=.050)	n/a
Gender Label	1404 (298)	1517 (304)	1444 (267)	5.10	p=.007	C>NR, C=R, R=NR
Gender Match	1275 (330)	1351 (327)	1339 (314)	ns	(p=.148)	n/a
Shape Match	1208 (260)	1213 (270)	1184 (222)	ns	(p=.835)	n/a

*All degrees of freedom: F(2,326)
**C=Control, NR=Non-Recovery, R=Recovery

Table 5. Conversion: Between-Group Differences in Activation

Activation Differences between Conversion, Non-Conversion, and Control Groups			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak voxel**
Affect Matching > Baseline			
Non-Converters > Converters			
15310	-22 28 -4	R amygdala, R parahippocampal gyrus, R hippocampus, R thalamus, R putamen, R lentiform nucleus, R insula, R ventrolateral PFC (BA 47), R inferior frontal gyrus (BA 45)	R parahippocampal gyrus
3345	-32 -82 -14	L middle occipital gyrus, L inferior occipital gyrus	L middle occipital gyrus
1678	-20 15 -16	L subcallosal gyrus, L insula, L middle frontal gyrus, L superior frontal gyrus, L ventrolateral PFC (BA 47)	L subcallosal gyrus
769	-32 -58 51	L superior parietal lobe, L inferior parietal lobe, L precuneus	L superior parietal lobe
756	-2 4 55	Bilateral superior frontal gyrus, L cingulate gyrus (BA 32), L medial frontal gyrus (BA 6)	L superior frontal gyrus
359	-40 1 31	L precentral gyrus, L insula (BA 13), L inferior frontal gyrus (BA 9)	L precentral gyrus
213	-28 -3 61	L middle frontal gyrus	L middle frontal gyrus
Converters > Non-Converters			
3052	12 -84 35	Bilateral cuneus	R cuneus
1160	18 37 -5	R ACC (BA 24, 32)	R ACC
457	-36 -34 11	L transverse temporal gyrus, L superior temporal gyrus (BA 41), L insula (BA 13)	L transverse temporal gyrus
441	-28 -48 15	L superior temporal gyrus, L middle temporal gyrus	L superior temporal gyrus
329	46 -13 10	R insula (BA 13), R superior temporal gyrus (BA 22, 41), R inferior parietal lobe	R insula
203	-18 60 34	L superior frontal gyrus (BA 9)	L superior frontal gyrus

Controls > Converters			
22482	24 -29 -6	R amygdala, R parahippocampal gyrus, R hippocampus, R thalamus, R putamen, R lentiform nucleus, R ventrolateral PFC, R inferior frontal gyrus (BA 45), R insula	R parahippocampal gyrus
1106	-2 6 57	Bilateral superior frontal gyrus (BA 6, 8), bilateral medial frontal gyrus	L superior frontal gyrus
603	-32 -58 51	L superior parietal lobe, L inferior parietal lobe	L superior parietal lobe
311	53 -2 -38	R inferior temporal gyrus, R middle temporal gyrus	R inferior temporal gyrus
Converters > Controls			
1403	12 -84 35	Bilateral cuneus	R cuneus
1320	16 37 -5	R ACC (32), R medial frontal gyrus (BA 10), R caudate	R ACC
1316	-14 -43 41	Bilateral cingulate gyrus, precuneus	L cingulate gyrus
987	46 -30 20	R insula (BA 13), R superior temporal gyrus (BA 22, 41)	R insula
708	-44 -24 -16	L fusiform gyrus, L middle temporal gyrus, L superior temporal gyrus	L fusiform gyrus
231	-10 -57 64	L precuneus, L postcentral gyrus (BA 40)	L precuneus
Controls > Non-Converters			
424	10 19 25	R ACC (BA 24)	R ACC
414	-10 -48 -36	Bilateral cerebellum	L cerebellum
403	20 -48 11	R posterior cingulate	R posterior cingulate
318	10 -81 2	R cuneus	R cuneus
263	-28 -50 15	L superior temporal gyrus	L superior temporal gyrus

206	-10 -30 20	L thalamus	L thalamus
Non-Converters > Controls			
468	42 -2 33	R inferior frontal gyrus (BA 6, 9, 44), R insula	R inferior frontal gyrus
286	-60 -16 8	L superior temporal gyrus	L superior temporal gyrus
266	-16 44 -9	L middle frontal gyrus, L superior frontal gyrus	L middle frontal gyrus
188	61 -28 31	R inferior parietal lobe (BA 40)	R inferior parietal lobe
Affect Labeling > Baseline			
Non-Converters > Converters			
2775	30 -92 -12	R inferior occipital gyrus (BA 18), R middle occipital gyrus	R inferior occipital gyrus
2168	-20 -101 1	L middle occipital gyrus (BA 18), L inferior occipital gyrus (BA 17)	L middle occipital gyrus
680	-55 -31 44	L postcentral gyrus (BA 2), L inferior parietal lobe (BA 40)	L postcentral gyrus
609	0 -51 -8	L cerebellum	L cerebellum
549	-2 21 -6	L ACC (BA 25)	L ACC
375	46 9 27	R inferior frontal gyrus (BA 9)	R inferior frontal gyrus
315	57 33 0	R ventrolateral PFC (BA 47, 45, 44)	R ventrolateral PFC
239	-28 -12 -1	L putamen, L lentiform nucleus, L lateral globus pallidus	L putamen
227	22 -8 -17	R amygdala, R parahippocampal gyrus	R amygdala
Converters > Non-Converters			
1483	12 -82 35	R cuneus (BA 19), R posterior cingulate	R cuneus

1174	-12 -41 41	Bilateral cingulate gyrus (BA 31)	L cingulate gyrus
425	-24 -47 -12	L parahippocampal gyrus (BA 37), L fusiform gyrus (BA 19)	L parahippocampal gyrus
281	38 -84 39	R precuneus	R precuneus
275	-30 22 53	L superior frontal gyrus (BA 8), L middle frontal gyrus (BA 9)	L superior frontal gyrus
Controls > Converters			
2474	46 -63 -32	R cerebellum, R inferior occipital gyrus, R middle occipital gyrus (BA 18)	R cerebellum
1556	-20 -101 1	L middle occipital gyrus (BA 18)	L middle occipital gyrus
1408	-24 -27 1	L thalamus	L thalamus
695	-55 -31 44	L postcentral gyrus (BA 2)	L postcentral gyrus
575	24 -7 -19	R amygdala, R parahippocampal gyrus	R amygdala
403	0 -51 -5	L cerebellum	L cerebellum
354	57 31 -1	R ventrolateral PFC (BA 47, 45, 44)	R ventrolateral PFC
303	46 9 27	R inferior frontal gyrus (BA 9)	R inferior frontal gyrus
221	16 -15 14	R thalamus	R thalamus
203	-2 21 -6	L ACC (BA 24, 25)	L ACC
Converters > Controls			
1461	12 -84 30	R cuneus, R posterior cingulate (BA 31)	R cuneus
1341	10 -47 39	Bilateral cingulate gyrus (BA 31)	R cingulate gyrus
515	-26 -47 -15	L fusiform gyrus	L fusiform gyrus

324	32 -56 -1	R middle occipital gyrus, R lingual gyrus	R middle occipital gyrus
238	-26 12 57	L superior frontal gyrus, L middle frontal gyrus	L superior frontal gyrus
237	36 -85 41	R precuneus	R precuneus
Controls > Non-Converters			
545	-24 -11 10	L putamen, L thalamus	L putamen
212	-36 51 20	L superior frontal gyrus	L superior frontal gyrus
Non-Converters > Controls			
374	-16 64 8	L medial frontal gyrus	L medial frontal gyrus
234	18 29 -5	R ACC	R ACC
226	-6 18 3	L caudate, L ACC	L caudate
199	-38 -56 -3	L middle temporal gyrus, L fusiform gyrus (BA 37)	L middle temporal gyrus
194	-32 -74 -7	L lingual gyrus, L inferior occipital gyrus	L lingual gyrus

Table 6. Conversion: Between-Group Differences in Functional Connectivity

Amygdala (Right) Functional Connectivity Group Differences			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak region**
Affect Labeling > Baseline			
Non-Converters > Converters			
229	-53 23 -1	L ventrolateral PFC (BA 47)	L ventrolateral PFC
156	-38 47 11	L inferior frontal gyrus (BA 46), L middle frontal gyrus	L middle frontal gyrus
115	0 37 45	R medial frontal gyrus	R medial frontal gyrus
100	-42 11 35	L middle frontal gyrus (BA 9)	L middle frontal gyrus
Controls > Converters			
223	-53 27 1	L ventrolateral PFC (BA 47)	L ventrolateral PFC
221	0 37 45	R medial frontal gyrus	R medial frontal gyrus
135	-46 13 35	L middle frontal gyrus	L middle frontal gyrus
112	55 17 25	R inferior frontal gyrus (BA 9)	R inferior frontal gyrus
Controls > Non-Converters			
155	16 30 21	R ACC (BA 32)	RACC
142	55 31 -10	R ventrolateral PFC (BA 47)	R ventrolateral PFC

Non-Converters > Controls			
243	-55 15 40	L middle frontal gyrus	L middle frontal gyrus
Affect Matching > Baseline			
Controls > Non-Converters			
219	-36 35 6	L ventrolateral PFC (BA 47, 45)	L ventrolateral PFC
146	-26 60 7	L superior frontal gyrus (BA 10)	L superior frontal gyrus
144	44 10 5	R ventrolateral PFC (BA 45), R insula (BA 13)	R insula
104	36 37 6	R inferior frontal gyrus, R middle frontal gyrus	R inferior frontal gyrus
95	34 15 29	R middle frontal gyrus	R middle frontal gyrus
Amygdala (Left) Functional Connectivity Group Differences			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak region**
Affect Labeling > Baseline			
Non-Converters > Converters			
123	-28 43 11	L inferior frontal gyrus, L middle frontal gyrus, L superior frontal gyrus	L superior frontal gyrus
115	0 37 45	R medial frontal gyrus	R medial frontal gyrus
106	-24 57 14	L ACC (BA 32), L medial frontal gyrus (BA 10), L superior frontal gyrus	L superior frontal gyrus
Controls > Converters			

444	0 37 45	R medial frontal gyrus	R medial frontal gyrus
275	-26 43 11	L ventrolateral PFC (BA 47), L inferior frontal gyrus, L superior frontal gyrus, L medial frontal gyrus	L superior frontal gyrus
122	-57 22 10	L ventrolateral PFC (BA 45)	L ventrolateral PFC
112	38 29 36	R middle frontal gyrus (BA 9)	R middle frontal gyrus
Controls > Non-Converters			
221	6 46 42	R medial frontal gyrus	R medial frontal gyrus
123	22 30 19	R ACC	R ACC
Affect Matching > Baseline			
Controls > Non-Converters			
1779	18 -20 34	R cingulate gyrus	R cingulate gyrus
723	30 9 -11	R ventrolateral PFC (BA 47), R insula	R inferior frontal gyrus
444	6 19 34	R cingulate gyrus (BA 32)	R cingulate gyrus
371	-26 59 10	L middle frontal gyrus (BA 10)	L middle frontal gyrus
111	-6 59 14	L medial frontal gyrus (BA 10)	L medial frontal gyrus
96	-2 40 20	L ACC (BA 32)	L ACC

Table 7. Recovery: Between-Group Differences in Activation

Activation Differences between Recovery Non-Recovery, and Control Groups			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak voxel**
Affect Matching > Baseline			
Recovery > Non-Recovery			
2315	36 1 17	R amygdala, R parahippocampal gyrus, R insula, R inferior frontal gyrus (BA 44), R superior temporal gyrus (BA 41)	R insula
3110	-4 21 40	Bilateral cingulate gyrus (BA 32, 24), L precuneus	L cingulate gyrus
1573	-4 -21 -30	Bilateral cerebellum, brainstem	Brainstem
583	44 45 15	R middle frontal gyrus (BA 10)	R middle frontal gyrus
524	-26 56 29	L superior frontal gyrus (BA 10)	
521	-48 -15 45	L precentral gyrus, L postcentral gyrus	L precentral gyrus
429	36 -18 -11	R caudate, R parahippocampal gyrus (BA 37), R fusiform gyrus	R caudate
416	14 -78 39	R precuneus	R precuneus
334	32 -38 59	R postcentral gyrus, R superior parietal lobe (BA 7)	R postcentral gyrus
299	-42 25 32	L middle frontal gyrus	L middle frontal gyrus
292	20 -45 -5	R lingual gyrus, R parahippocampal gyrus	R lingual gyrus
288	-34 25 -1	L ventrolateral PFC (BA 47)	L ventrolateral PFC
273	32 32 30	R middle frontal gyrus	R middle frontal gyrus

236	2 -12 26	R cingulate gyrus, R thalamus	R cingulate gyrus
Controls > Recovery			
469	4 -86 -10	R lingual gyrus (BA 18), R cuneus (BA 30)	R lingual gyrus
191	-18 59 10	L superior frontal gyrus, L medial frontal gyrus	L superior frontal gyrus
Recovery > Controls			
2069	36 1 17	R insula (BA 13), R inferior frontal gyrus (BA 44), R postcentral gyrus, R superior temporal gyrus (BA 41)	R insula
1718	-38 -26 20	L insula (BA 13), L superior temporal gyrus	L insula
1083	-40 -27 38	L precentral gyrus, L inferior parietal lobe (BA 40)	L precentral gyrus
383	40 -38 61	R postcentral gyrus (BA 5), R superior parietal lobe (BA 7)	R postcentral gyrus
360	16 -80 35	R precuneus (BA 7)	
335	-44 9 22	L inferior frontal gyrus (BA 9)	L inferior frontal gyrus
312	-14 -41 41	L cingulate gyrus	L cingulate gyrus
305	53 -19 47	R postcentral gyrus	R postcentral gyrus
279	-8 2 35	L cingulate gyrus (BA 24)	L cingulate gyrus
Controls > Non-Recovery			
2939	-10 -48 -34	Bilateral cerebellum	L cerebellum
964	18 -48 6	R posterior cingulate, R parahippocampal gyrus	R posterior cingulate
423	-4 -17 6	Bilateral thalamus	L thalamus

395	-34 20 18	L insula (BA 13), L ventrolateral PFC (BA 47)	L insula
386	16 -5 -17	R amygdala, parahippocampal gyrus (BA 28, 34)	R parahippocampal gyrus
350	-4 21 40	L cingulate gyrus (BA 32)	L cingulate gyrus
289	16 -70 1	R lingual gyrus	R lingual gyrus
210	-12 -61 29	L precuneus (BA 31), cuneus (BA 7)	L precuneus
196	16 -70 35	R precuneus	R precuneus
Non-Recovery > Controls			
238	63 5 22	R inferior frontal gyrus (BA 9), R precentral gyrus (BA 6)	R inferior frontal gyrus
Affect Labeling > Baseline			
Recovery > Non-Recovery			
4402	6 -8 -5	Bilateral thalamus, R hypothalamus, bilateral insula, L putamen	R thalamus
1805	32 0 39	R precentral gyrus, bilateral ACC (BA 24, BA 32), bilateral medial frontal gyrus, bilateral cingulate gyrus, R middle frontal gyrus	R precentral gyrus
963	-10 -29 53	L paracentral lobule, L precuneus, L cingulate gyrus	L paracentral lobule
953	46 27 -10	R ventrolateral PFC (BA 47), R middle frontal gyrus	R ventrolateral PFC
575	-22 4 39	L cingulate gyrus, L superior frontal gyrus (BA 8)	L cingulate gyrus
569	57 -32 -19	R middle temporal gyrus	R middle temporal gyrus
554	-42 -36 11	L superior temporal gyrus (BA 41), L supramarginal gyrus, L inferior parietal lobe	L superior temporal gyrus
521	10 -45 -12	R cerebellum	R cerebellum

404	-28 57 18	L superior frontal gyrus (BA 10), L middle frontal gyrus	L superior frontal gyrus
334	-6 -65 23	L precuneus, L posterior cingulate (BA 31)	L precuneus
258	46 -32 29	R inferior parietal lobe, R postcentral gyrus	R inferior parietal lobe
219	-26 -45 -17	L cerebellum, L parahippocampal gyrus (BA 37)	L cerebellum
Recovery > Controls			
3160	-16 61 10	Bilateral ventrolateral PFC (BA 47), bilateral ACC (BA32, 24), L medial frontal gyrus, L superior frontal gyrus	L superior frontal gyrus
764	-38 -47 32	L supramarginal gyrus, L inferior parietal lobe (BA 40)	L supramarginal gyrus
762	14 -37 31	Bilateral cingulate gyrus, L posterior cingulate (BA 31), L precuneus	R cingulate gyrus
551	18 -46 -31	Bilateral cerebellum	R cerebellum
538	6 -8 -5	Bilateral thalamus, R lentiform nucleus	R thalamus
536	-22 18 49	L middle frontal gyrus, L medial frontal gyrus	L middle frontal gyrus
462	-36 -27 -4	L caudate, L superior temporal gyrus, L inferior temporal gyrus	L caudate
375	28 18 49	R middle frontal gyrus, R precentral gyrus	R middle frontal gyrus
330	8 43 44	Bilateral medial frontal gyrus (BA 6)	R medial frontal gyrus
251	32 -40 -21	R fusiform gyrus (BA 20, 37)	R fusiform gyrus
226	-24 -63 62	L superior parietal lobe (BA 7), L precuneus	L superior parietal lobe
205	59 0 -5	R superior temporal gyrus, R middle temporal gyrus	R superior temporal gyrus
191	32 0 39	R precentral gyrus, R cingulate gyrus	R precentral gyrus

Controls > Non-Recovery			
699	-20 -11 19	L thalamus, L putamen, L lentiform nucleus	L thalamus
350	34 37 6	R inferior frontal gyrus (BA 46), R middle frontal gyrus	R inferior frontal gyrus
277	44 12 46	R middle frontal gyrus	R middle frontal gyrus
215	-38 51 18	L superior frontal gyrus (BA 10)	L superior frontal gyrus
Non-Recovery > Controls			
207	-16 64 8	L medial frontal gyrus (BA 10)	L medial frontal gyrus

Table 8. Recovery: Between-Group Differences in Functional Connectivity

Amygdala (Right) Functional Connectivity Group Differences			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak region**
Affect Labeling > Baseline			
Recovery > Non-Recovery			
242	51 36 -10	R ventrolateral PFC (BA 47)	R ventrolateral PFC
221	44 21 29	R middle frontal gyrus, R inferior frontal gyrus (BA 9)	R middle frontal gyrus
172	4 4 -7	R ACC (BA 25), R putamen, R caudate	R ACC
Non-Recovery > Recovery			
128	-18 36 30	L medial frontal gyrus (BA 9)	L medial frontal gyrus
Controls > Recovery			
278	12 38 17	R ACC (BA 32)	R ACC
261	-18 59 25	L superior frontal gyrus (BA 10), L middle frontal gyrus	L superior frontal gyrus
143	-8 54 -6	L medial frontal gyrus	L medial frontal gyrus
103	18 43 44	R superior frontal gyrus	R superior frontal gyrus
94	10 44 28	R medial frontal gyrus	R medial frontal gyrus

Recovery > Controls			
372	-55 15 38	L middle frontal gyrus, L inferior frontal gyrus (BA 9)	L middle frontal gyrus
143	38 19 34	R middle frontal gyrus	R middle frontal gyrus
Controls > Non-Recovery			
264	53 34 -12	R ventrolateral PFC (BA 47)	R ventrolateral PFC
104	20 64 4	R superior frontal gyrus (BA 10)	R superior frontal gyrus
Non-Recovery > Controls			
196	-55 15 40	L middle frontal gyrus	L middle frontal gyrus
Affect Matching > Baseline			
Recovery > Non-Recovery			
434	-20 40 35	L medial frontal gyrus, LACC (BA 32), L superior frontal gyrus	L superior frontal gyrus
154	-20 16 51	L superior frontal gyrus (BA 8)	L superior frontal gyrus
147	0 27 30	L ACC (BA 24), L cingulate gyrus	L cingulate gyrus
Non-Recovery > Recovery			
113	24 44 -5	R middle frontal gyrus	R middle frontal gyrus
101	-18 36 -10	L middle frontal gyrus	L middle frontal gyrus

Controls > Recovery			
165	53 33 -10	R ventrolateral PFC (BA 47)	R ventrolateral PFC
136	26 58 5	R superior frontal gyrus (BA 10)	R superior frontal gyrus
Recovery > Controls			
249	-14 36 32	L medial frontal gyrus	L medial frontal gyrus
Controls > Non-Recovery			
154	2 21 36	R ACC (BA 24), R cingulate gyrus	R cingulate gyrus
140	-30 58 5	L superior frontal gyrus (BA 10)	L superior frontal gyrus
110	34 15 29	R middle frontal gyrus	R middle frontal gyrus
Amygdala (Left) Functional Connectivity Group Differences			
Voxels	**Peak voxel (MNI)**	**Region**	**Location of peak region**
Affect Labeling > Baseline			
Recovery > Non-Recovery			
512	44 21 27	R middle frontal gyrus, R insula, R inferior frontal gyrus, R ventrolateral PFC (BA 45)	R middle frontal gyrus
338	-24 19 25	L middle frontal gyrus	L middle frontal gyrus
132	51 36 -10	R ventrolateral PFC (BA 47)	R ventrolateral PFC

123	10 59 25	R superior frontal gyrus	R superior frontal gyrus
Non-Recovery > Recovery			
229	2 50 -11	R ACC (BA 32), R medial frontal gyrus	R medial frontal gyrus
208	2 13 35	R cingulate gyrus, R ACC	R cingulate gyrus
Controls > Recovery			
515	12 38 19	R ACC (BA 32)	R ACC
475	10 44 28	R medial frontal gyrus	R medial frontal gyrus
123	-36 28 28	L middle frontal gyrus	L middle frontal gyrus
96	44 6 5	R ventrolateral PFC (BA 45), R insula (BA 13)	R insula
Recovery > Controls			
177	38 19 34	R middle frontal gyrus	R middle frontal gyrus
Controls > Non-Recovery			
166	2 52 35	R superior frontal gyrus	R superior frontal gyrus
150	4 70 8	R medial frontal gyrus (BA 10)	R medial frontal gyrus
Non-Recovery > Controls			

104	26 44 -14	R middle frontal gyrus (BA 11)	R middle frontal gyrus
Affect Matching > Baseline			
Recovery > Non-Recovery			
635	-24 29 43	L middle frontal gyrus (BA 8)	L middle frontal gyrus
194	14 13 38	R cingulate gyrus (BA 32)	R cingulate gyrus
121	-18 20 51	L superior frontal gyrus (BA 8), L medial frontal gyrus (BA 32)	L superior frontal gyrus
115	20 40 28	R medial frontal gyrus	R medial frontal gyrus
Controls > Recovery			
275	-32 54 1	L middle frontal gyrus (BA 10)	L middle frontal gyrus
238	18 -22 31	R cingulate gyrus	R cingulate gyrus
118	32 27 4	R inferior frontal gyrus, R insula	R inferior frontal gyrus
113	26 58 3	R superior frontal gyrus (BA 10)	R superior frontal gyrus
Recovery > Controls			
191	-8 43 44	L medial frontal gyrus	L medial frontal gyrus
Controls > Non-Recovery			
701	-12 33 41	L medial frontal gyrus	L medial frontal gyrus

408	-24 59 10	L middle frontal gyrus	L middle frontal gyrus
309	30 9 -11	R inferior frontal gyrus, R putamen	R inferior frontal gyrus
247	38 25 -6	R ventrolateral PFC (BA 47)	R ventrolateral PFC
149	-2 2 46	Bilateral cingulate gyrus (BA 24)	L cingulate gyrus
95	-12 61 18	L superior frontal gyrus	L superior frontal gyrus

Figure 1. Task Paradigm. During the fMRI task participants viewed emotional facial expressions and were asked to perform one of the following tasks: affect labeling, affect matching, gender labeling, gender matching, and shape matching (adapted from Lieberman et al., 2007).

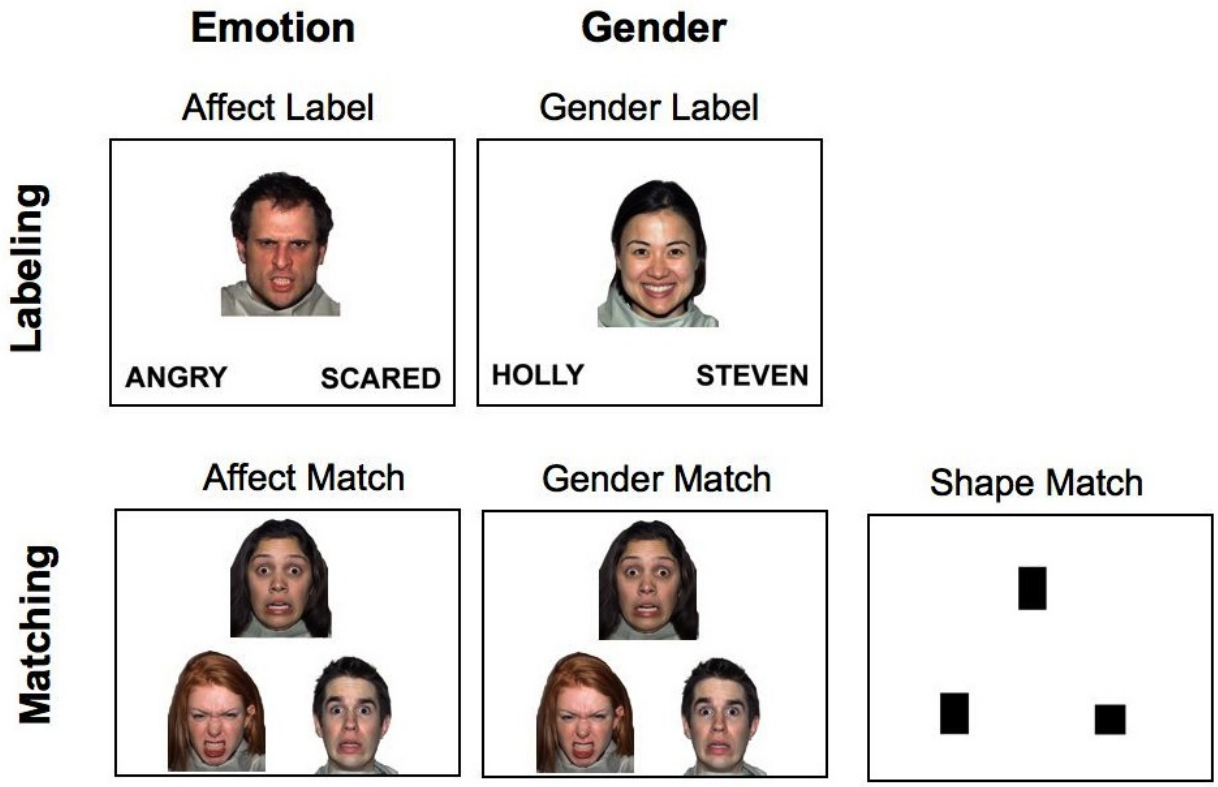


Figure 2. Accuracy and Conversion. Analyses of accuracy on responded trials demonstrated a main effect of condition and a condition-by-group interaction. Converters performed with the lowest accuracy overall (mean=93%, S.D.=10.9), and accuracy for non-converters (mean=95.5%, S.D.=2.6) was intermediate between converters and controls (mean=97.1%, S.D.=2.6). Affect matching was associated with the lowest accuracy overall. For the emotion-processing conditions, converters performed more poorly on affect matching than the other groups but did not differ significantly for affect labeling.

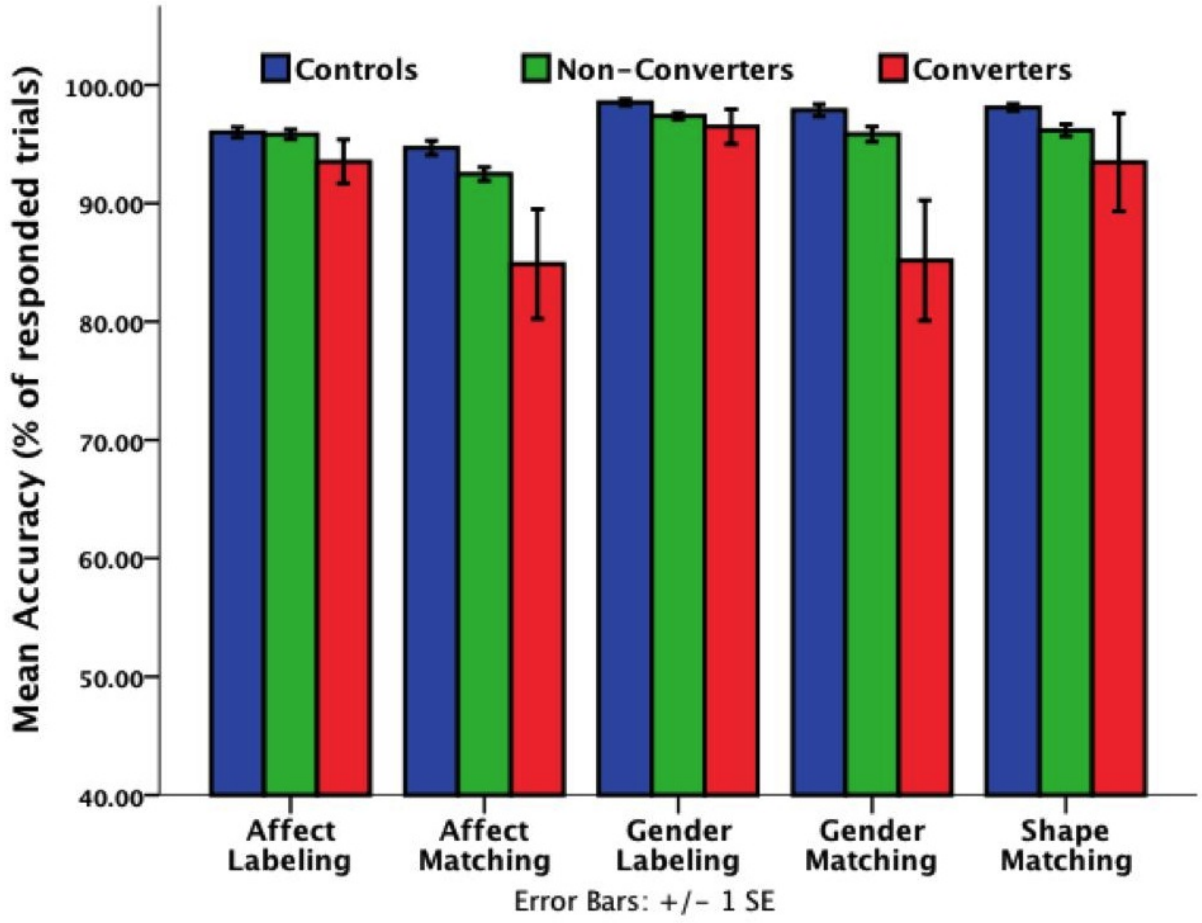


Figure 3. Accuracy and Recovery. Analyses of accuracy on responded trials showed main effects of condition and group. Across all participants, accuracy was lowest for affect matching. The recovery group performed with a mean accuracy of 95.44% (S.D.=5.33), which did not differ from the non-recovery or controls groups. Accuracy was significantly higher for the control group than the non-recovery group overall and on all conditions, with the exception of affect labeling, which was not associated with any group differences.

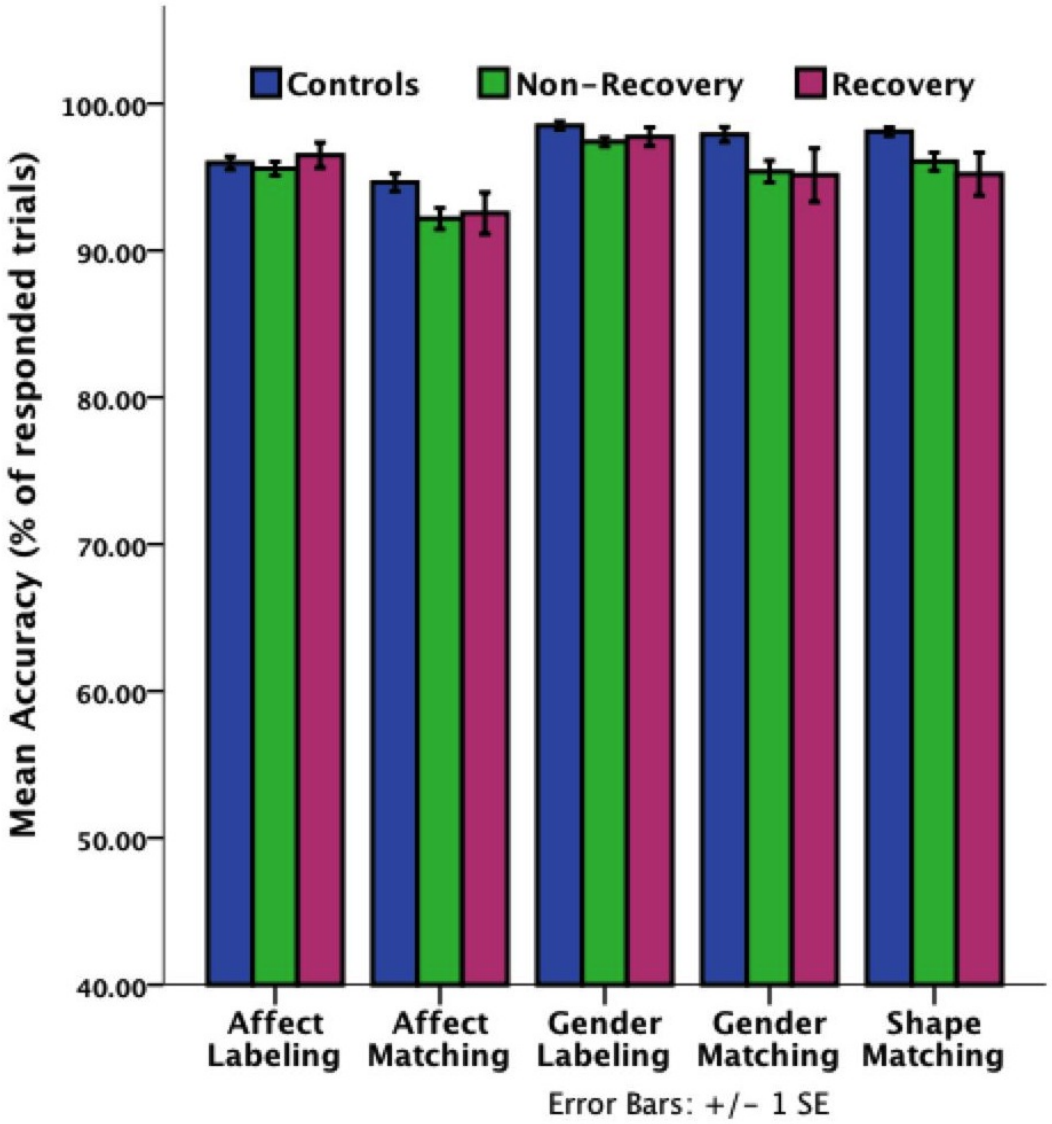


Figure 4. Reaction Time and Conversion. Analyses of reaction time showed main effects of group and condition. Overall mean reaction time was slower for converters than controls (p=.018) but did not significantly differ from non-converters (p=.130). Across all groups, reaction time was slowest for affect matching.

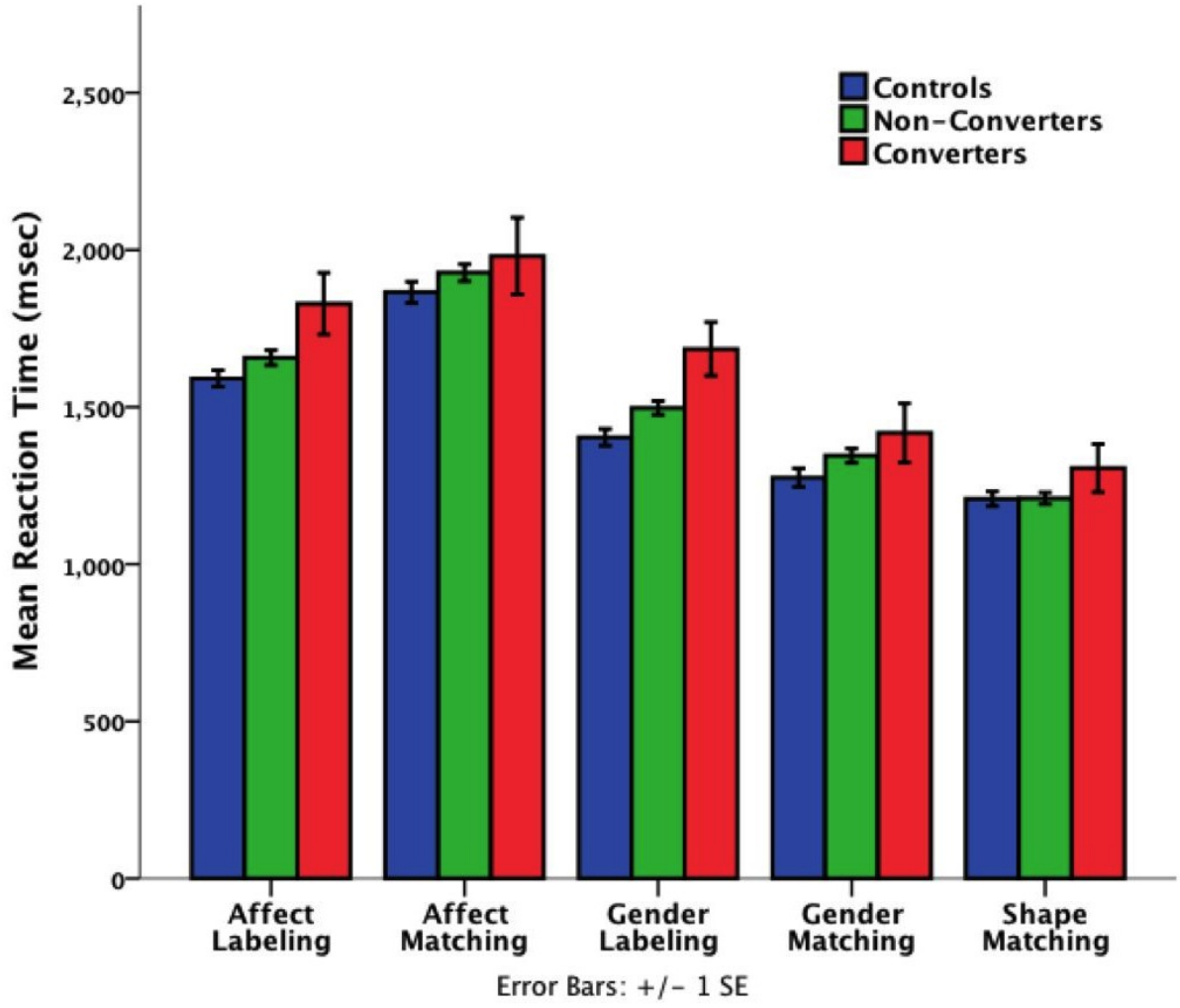


Figure 5. Reaction Time and Recovery. Analyses of reaction time demonstrated a main effect of condition, such that participants were slowest during affect matching and fastest during shape matching. The recovery group did not differ from the non-recovery or control groups on any of the conditions.

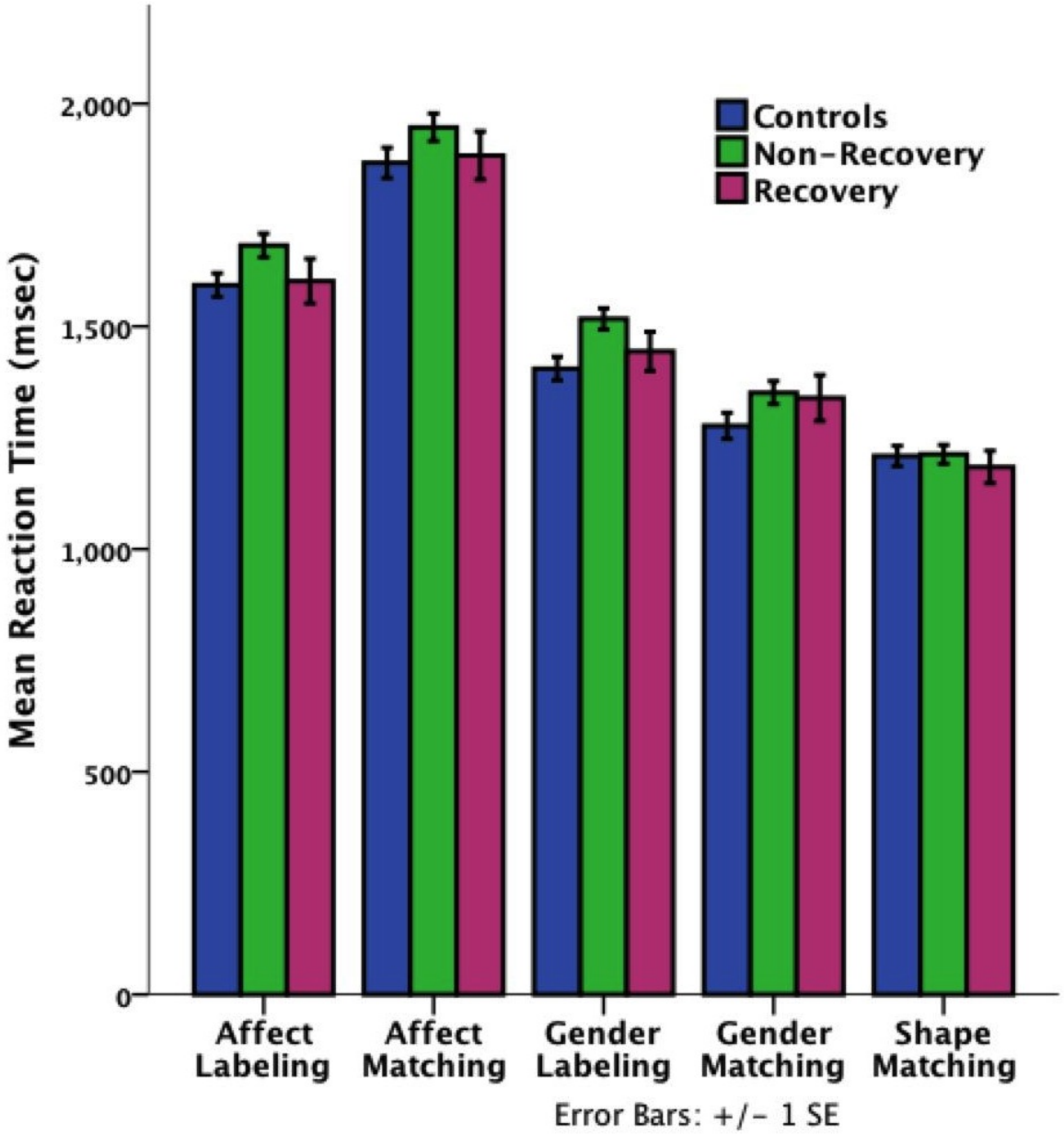


Figure 6. Amygdala Activation and Conversion. Relative to non-converters, converters displayed reduced activation in the amygdala during affect matching (p<.0001, corrected) and affect labeling (p=.011, corrected), relative to implicit baseline. Functional masks were created based on the group difference to extract percent signal change for illustration purposes. Because the region for group differences during affect matching also included regions such as parahippocampal gyrus and hippocampus, the functional mask for affect matching was created at p=.01 to isolate the cluster based on the local maxima in the amygdala.

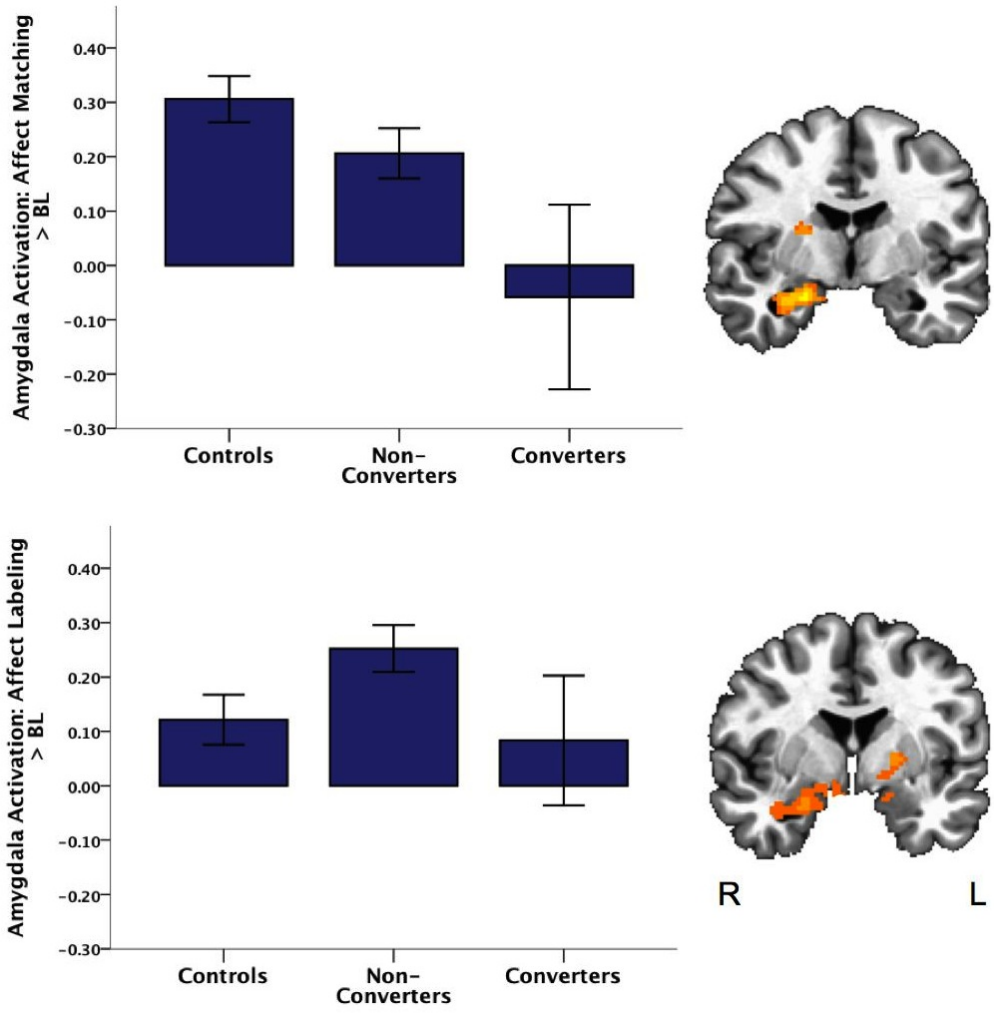


Figure 7. Ventrolateral PFC Activation and Conversion. Compared with non-converters and controls, converters showed reduced activation in ventrolateral PFC during affect labeling (p=.0003, corrected) and affect matching (p<.0001, corrected), relative to implicit baseline. Because the cluster identified for affect matching included other regions, the functional mask for affect matching was created at p=.02 to isolate the vlPFC based on its local maxima.

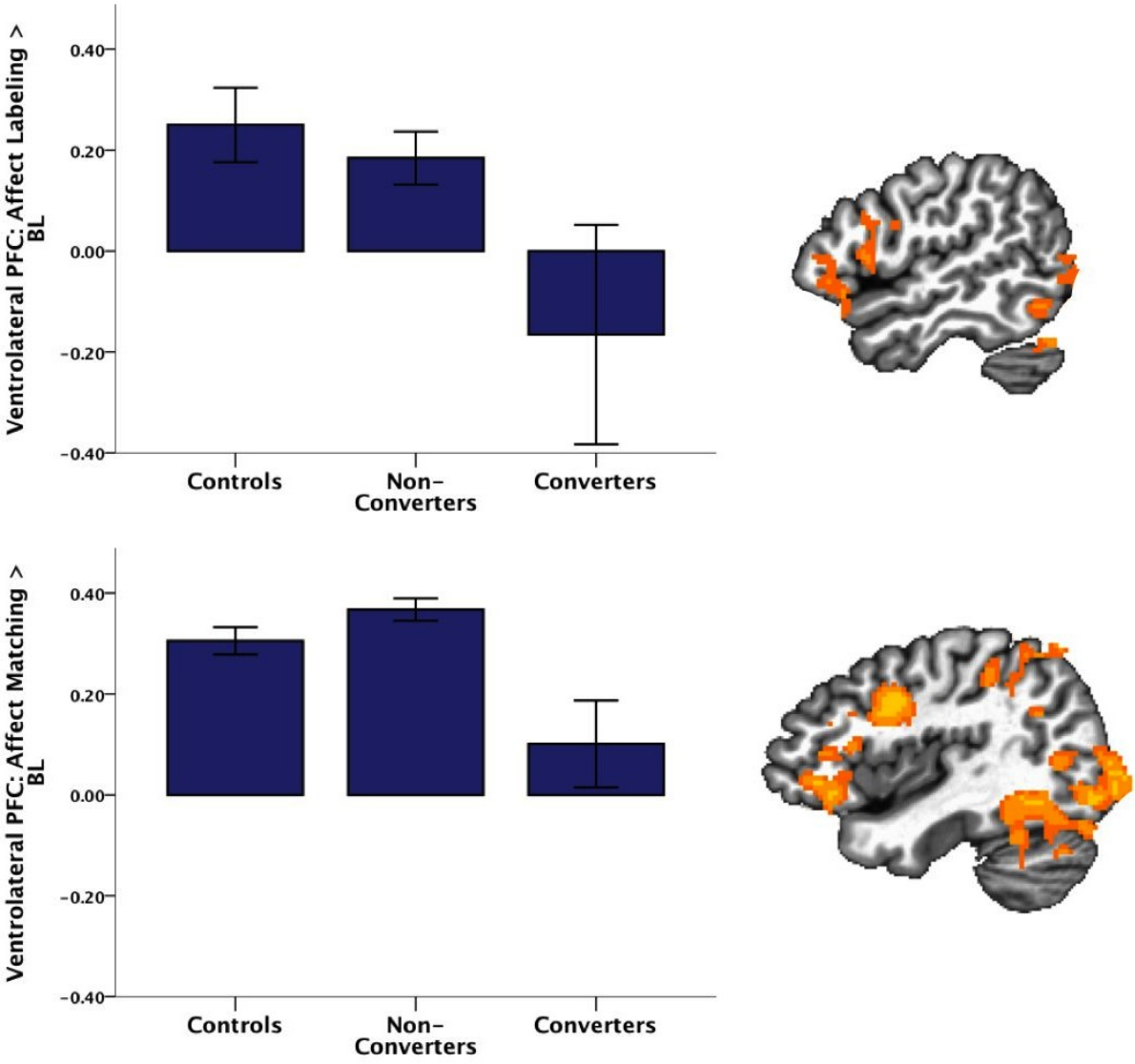


Figure 8. ACC Activation and Conversion. Converters showed relatively greater activation in ACC (BA 32) during affect matching compared with implicit baseline, relative to non-converters and controls ($p<.0001$, corrected). There were no group differences in ACC for affect labeling, as converters showed showed deactivation to a similar extent as controls and non-converters during affect labeling.

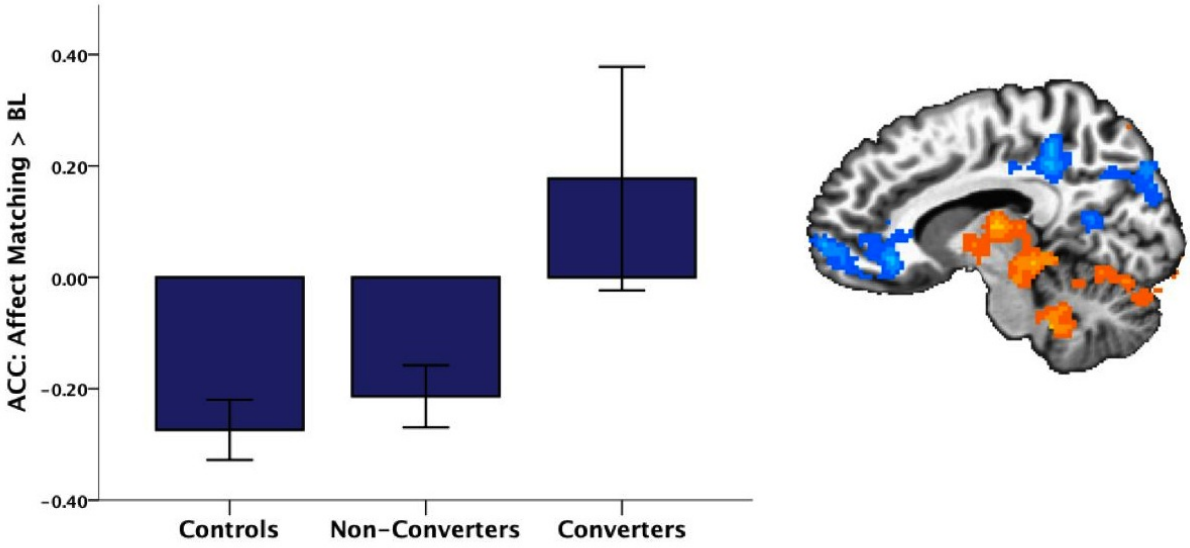


Figure 9. Amygdala-Ventrolateral PFC Functional Connectivity and Conversion. Converters showed significantly different functional connectivity between the amygdala and ventrolateral PFC compared with non-converters and controls during affect labeling (relative to implicit baseline; p<.0001, corrected). Specifically, converters displayed positive amygdala-ventrolateral PFC coupling, whereas controls and non-converters displayed negative and non-significant coupling, respectively.

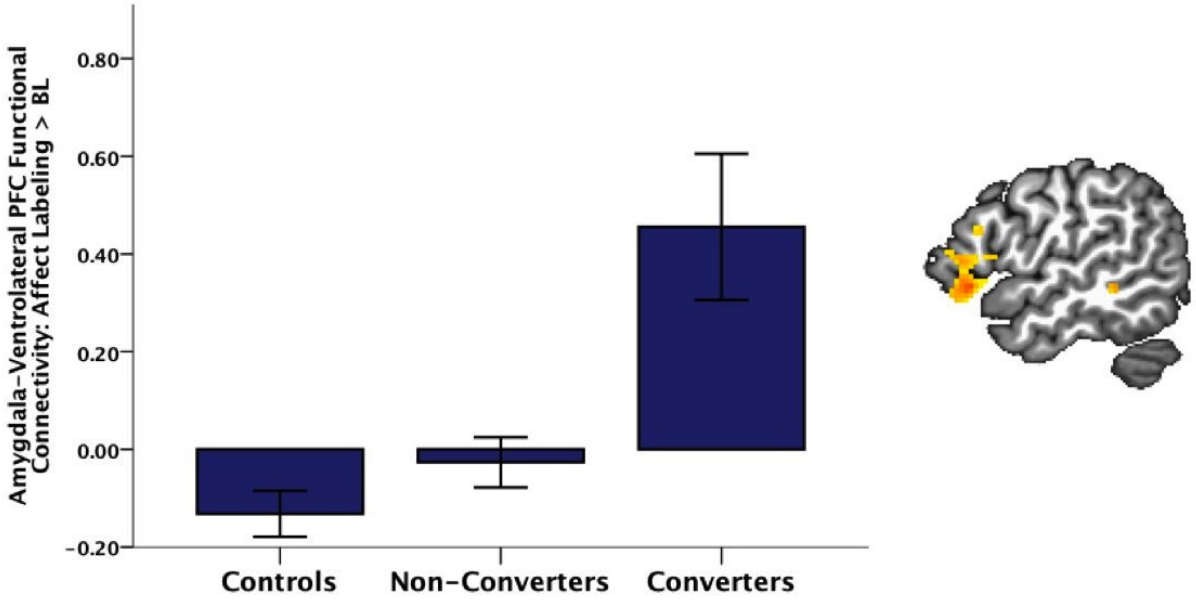


Figure 10. Amygdala-IFG Functional Connectivity and Conversion. Relative to non-converters and controls, converters displayed altered functional connectivity between the amygdala and inferior frontal gyrus (IFG) and middle frontal gyrus during affect labeling (p=.001, corrected). Converters displayed positive coupling whereas controls and non-converters displayed non-significant and negative coupling, respectively.

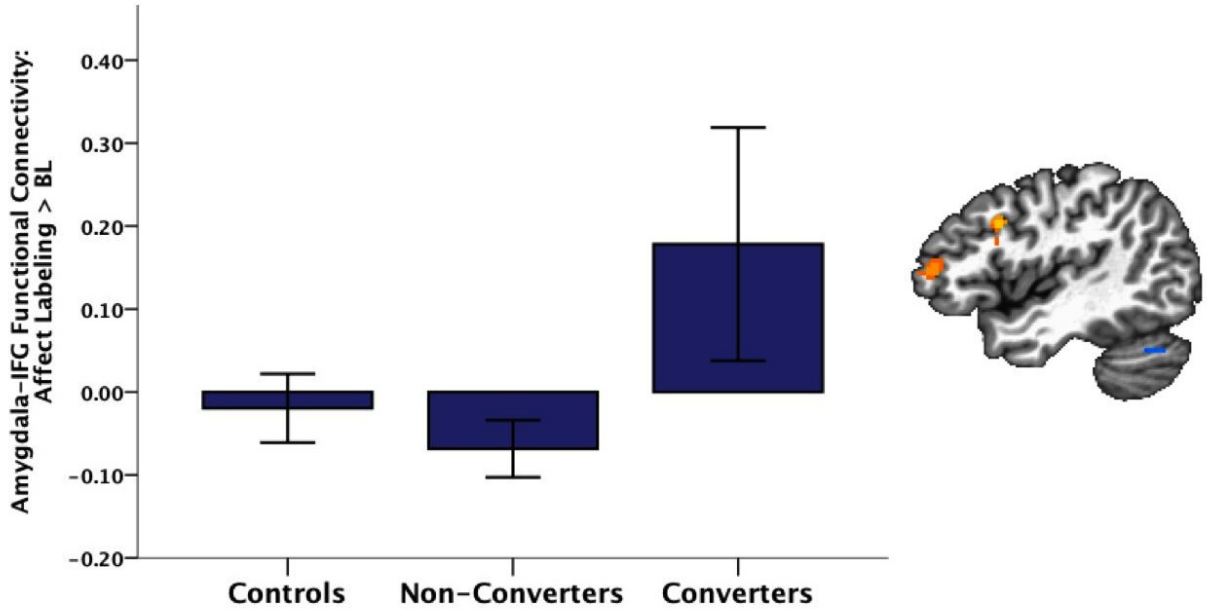


Figure 11. Amygdala-ACC Functional Connectivity and Conversion. Compared with non-converters and controls, converters displayed altered functional connectivity between the amygdala and ACC (p=.021, corrected). Converters displayed positive amygdala-ACC coupling, whereas controls and non-converters showed non-significant and negative coupling, respectively.

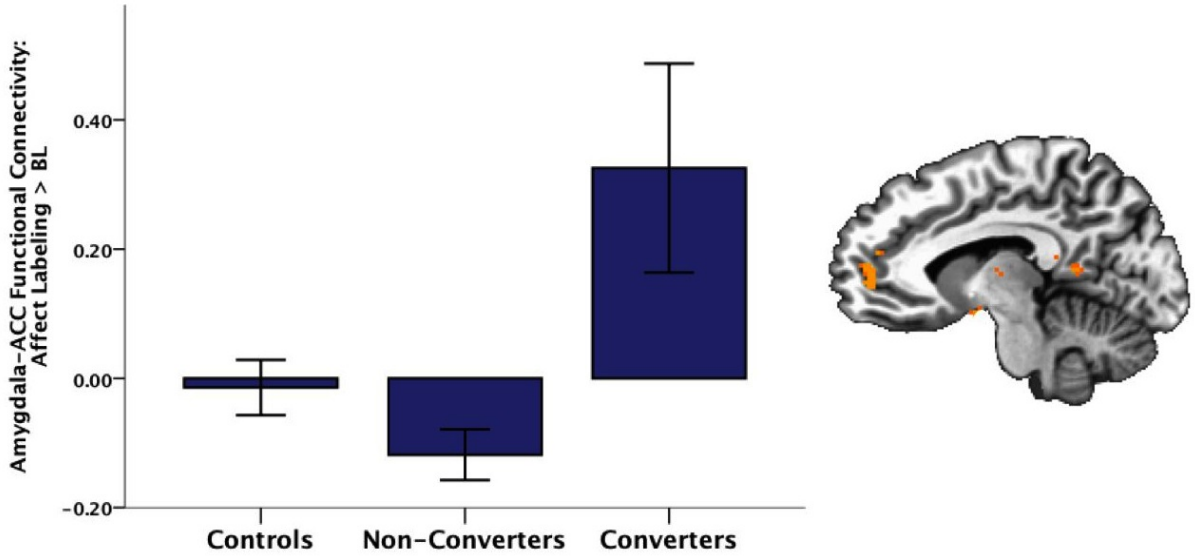


Figure 12. Age-Related Changes in Activation and Conversion. Converters showed an age-related decrease in ventrolateral PFC activation during affect labeling (left) and affect matching (middle), relative to implicit baseline. In addition, converters showed an age-related increase in ACC activation during affect matching (right), relative to implicit baseline. In contrast, non-converters and controls did not show significant age-related changes in these regions.

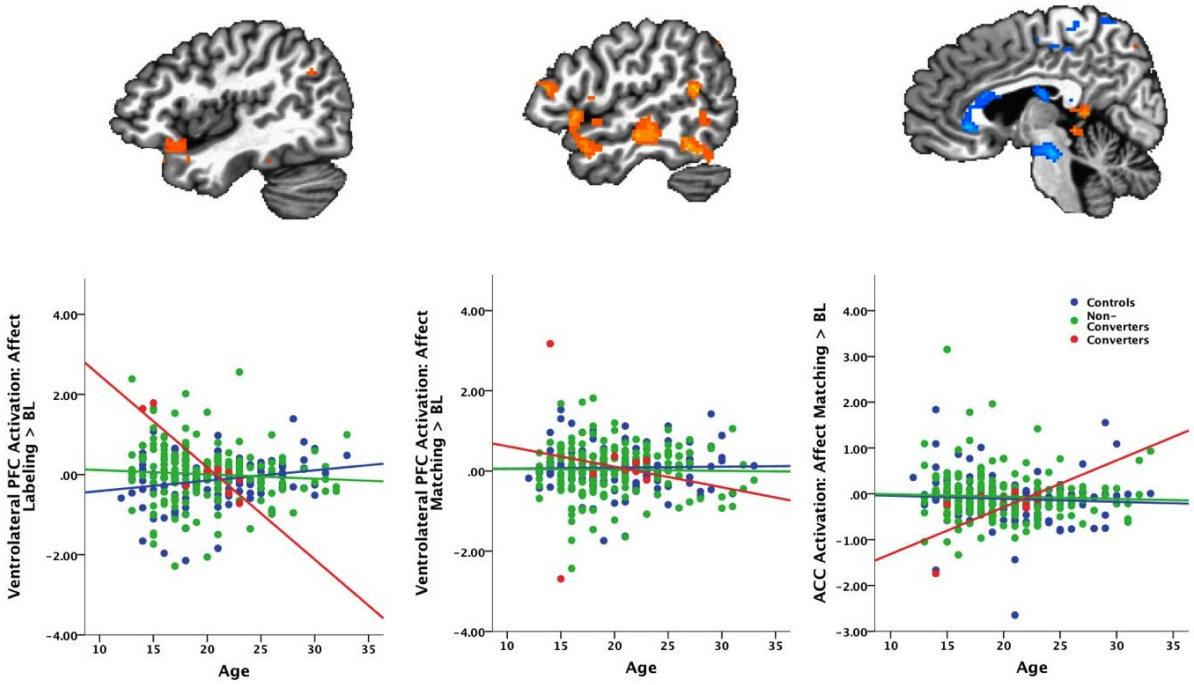


Figure 13. Age-Related Change in Functional Connectivity and Conversion. Converters exhibited an age-related increase in amygdala-ACC functional connectivity. The region of connectivity extended from bilateral ACC (BA 32) to bilateral medial frontal gyrus (BA 10). In contrast, non-converters and controls did not show significant age-related change.

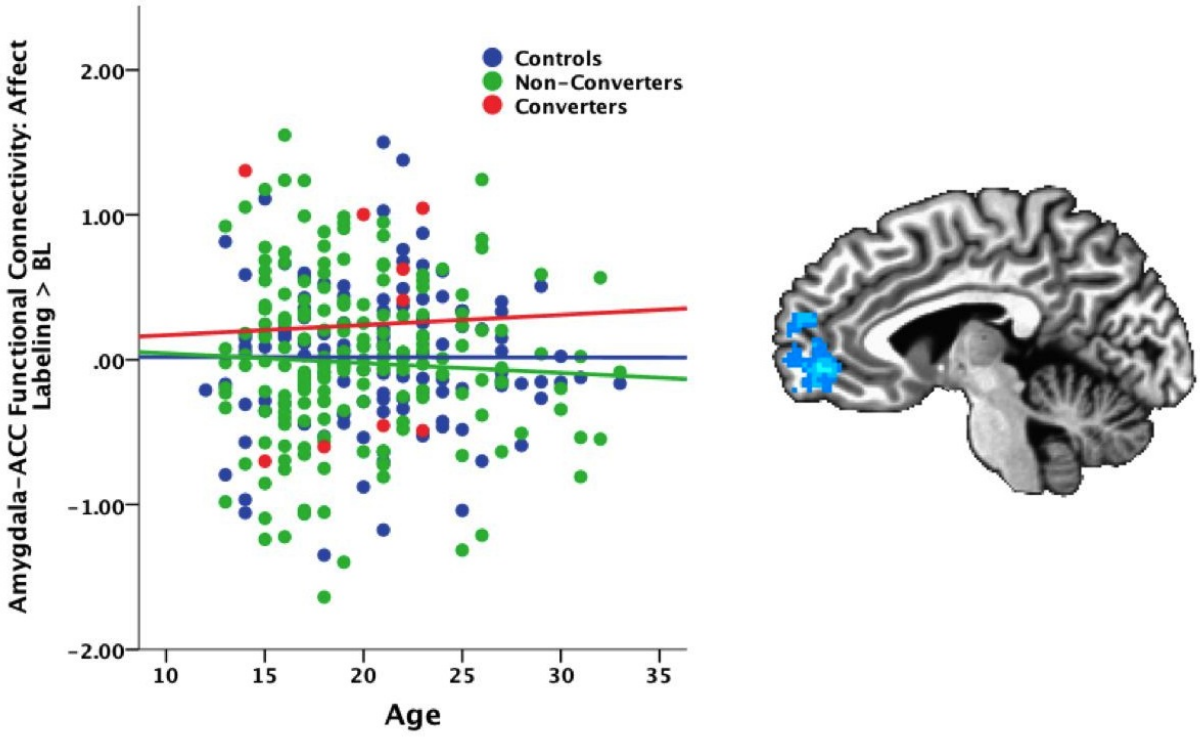


Figure 14. Ventrolateral PFC Activation and Time to Conversion. Within the converter group, ventrolateral PFC activation during affect labeling and affect matching predicted time to conversion, over and above the effects of age, sex, and percent of responded trials (F(8)=11.76, p=.027). Participants with lower prefrontal activation tended to converter earlier than participants with higher activation.

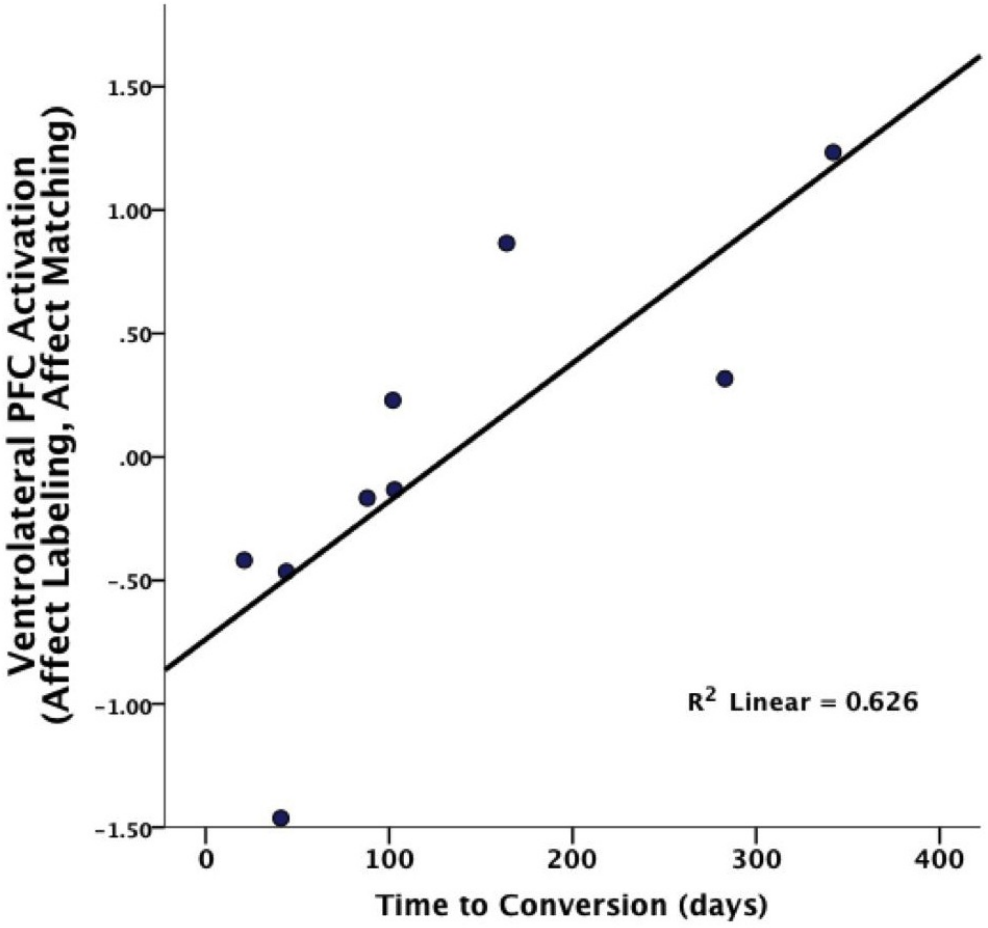


Figure 15. Amygdala Activation and Recovery. Compared with the non-recovery group, the recovery group had higher activation in the amygdala for affect matching (relative to implicit baseline; p<.0001, corrected). The recovery group did not differ from the control group. The functional mask for affect matching was thresholded at p=03 to isolate the amygdala based on its local maxima. There were no group differences for affect labeling.

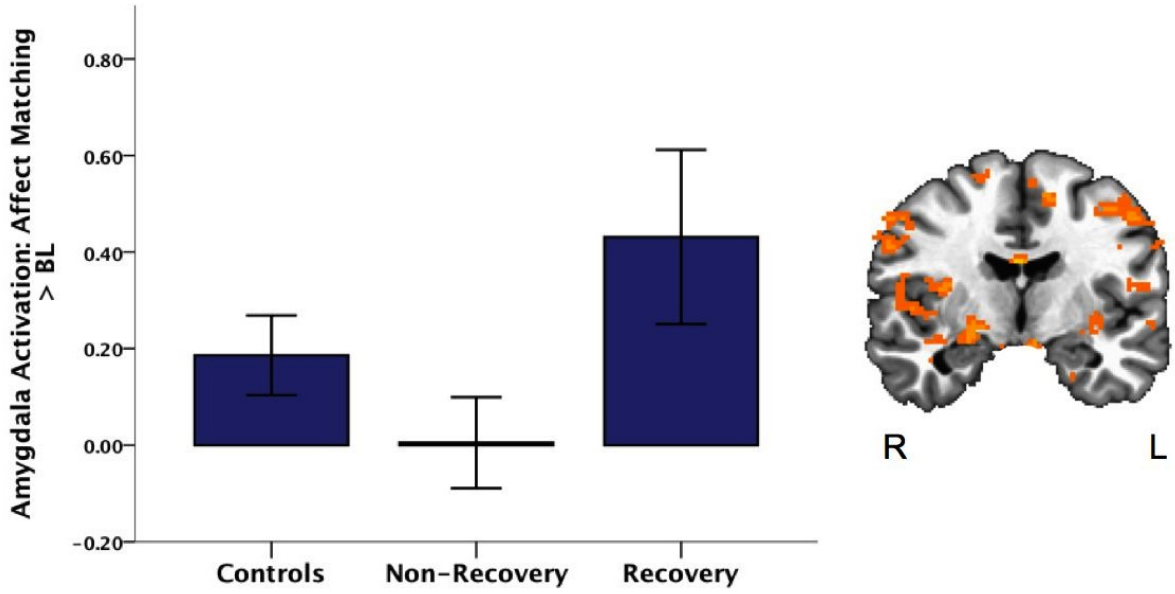


Figure 16. Ventrolateral PFC Activation and Conversion. Converters displayed greater activation in the ventrolateral PFC than non-converters during affect labeling (p<.0001, corrected) and affect matching (p=.0009, corrected), relative to implicit baseline. Ventrolateral PFC activation in converters was also higher than controls for the labeling condition.

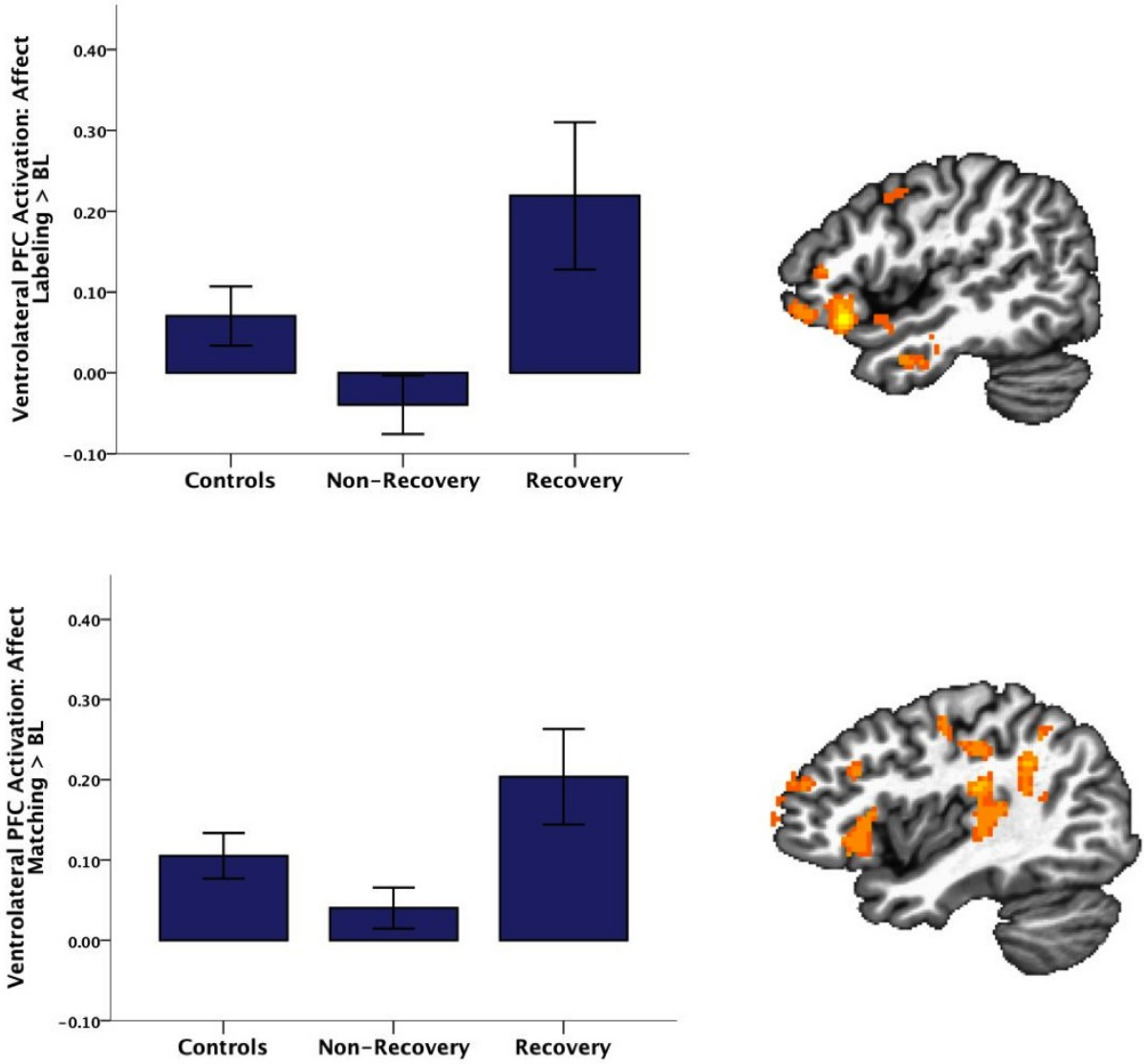


Figure 17. ACC Activation and Recovery. The recovery group displayed relatively greater activation in ACC (BA 32, 24) for affect labeling, compared with the non-recovery and control groups ($p<.0001$, corrected). There were no group differences for affect matching relative to implicit baseline, during which all groups deactivated ACC to a similar extent.

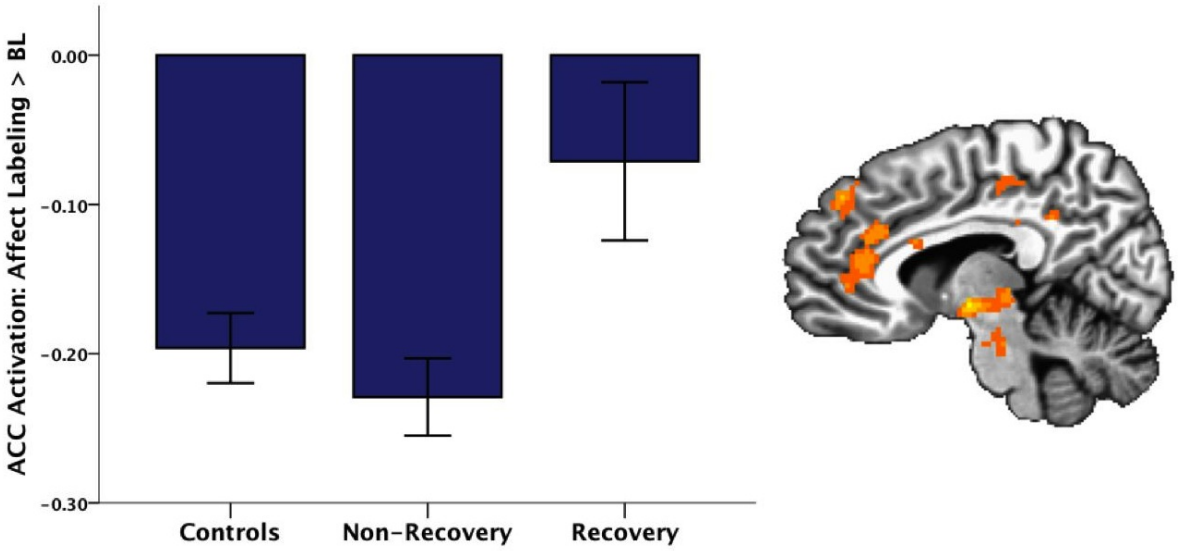


Figure 18. Amygdala-Ventrolateral PFC Functional Connectivity and Recovery. For affect labeling relative to implicit baseline, the recovery group displayed stronger functional connectivity between the amygdala and ventrolateral PFC than the non-recovery group ($p<.0001$, corrected). Functional connectivity was negative in the recovery group, which paralleled the expected pattern of negative amygdala-prefrontal coupling observed in the control group.

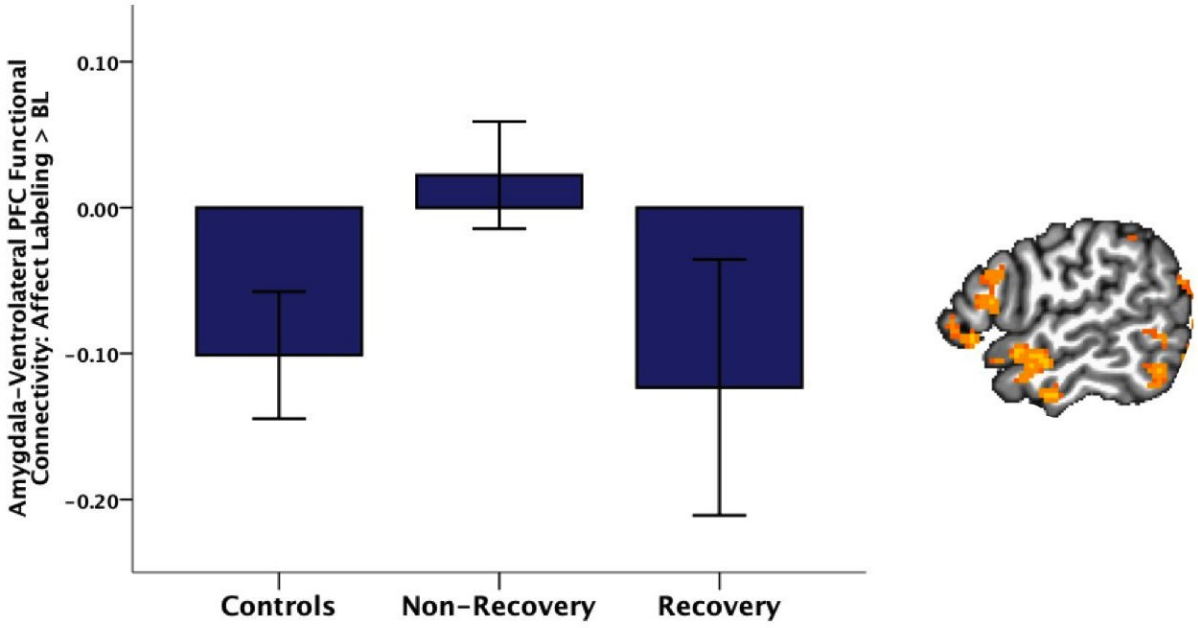


Figure 19. Amygdala-sgACC Functional Connectivity and Recovery. During affect labeling, the recovery group exhibited stronger negative functional connectivity between the amygdala and subgenual ACC (sgACC) than the non-recovery and control groups (p=.0002, corrected). The peak voxel was located in BA 25, and the cluster also included putamen and caudate.

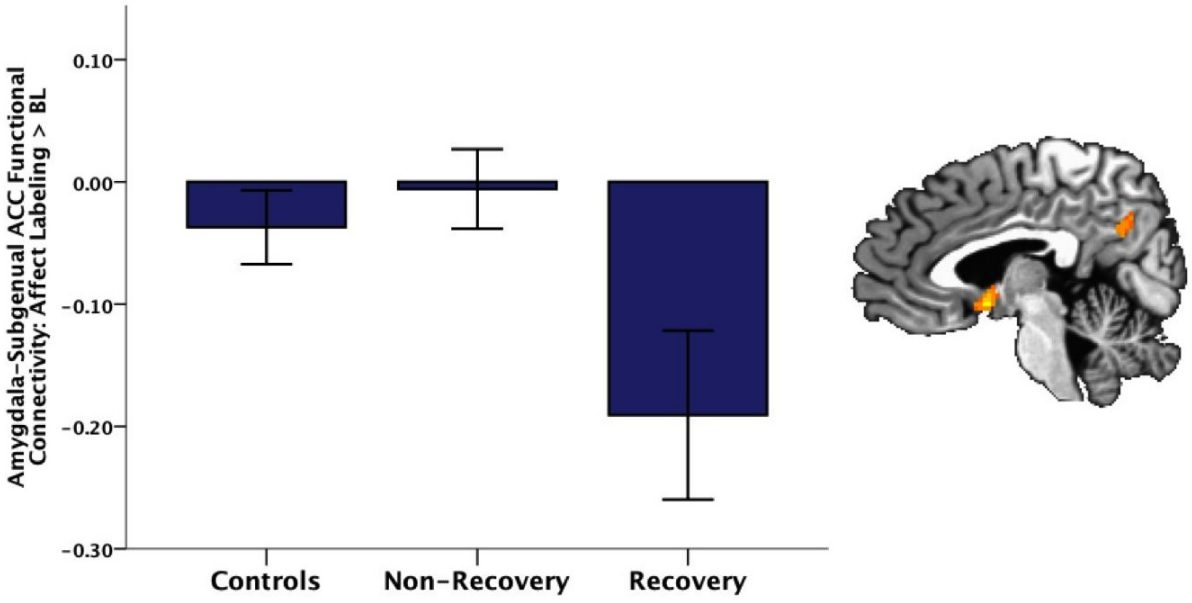


Figure 20. Amygdala-ACC Functional Connectivity and Recovery. Compared with the non-recovery and control groups, the recovery group displayed altered functional connectivity between the amygdala and ACC for affect labeling (relative to implicit baseline; $p<.0001$, corrected). While the control group displayed an expected pattern of negative coupling, the recovery group showed positive amygdala-ACC coupling.

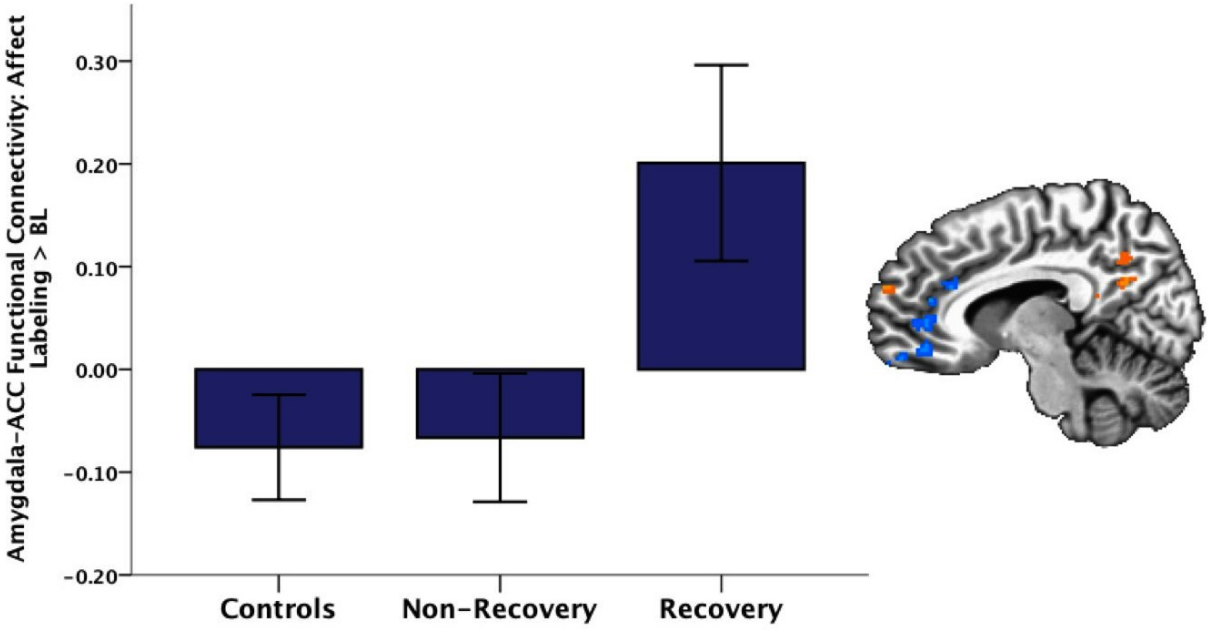


Figure 21. Age-Related ACC Activation and Recovery. For affect labeling relative to implicit baseline, the recovery group demonstrated an age-related increase in ACC activation, which differed from an age-related decrease in ACC activation in the non-recovery group (p=.027, corrected). The recovery group did not significantly differ from controls.

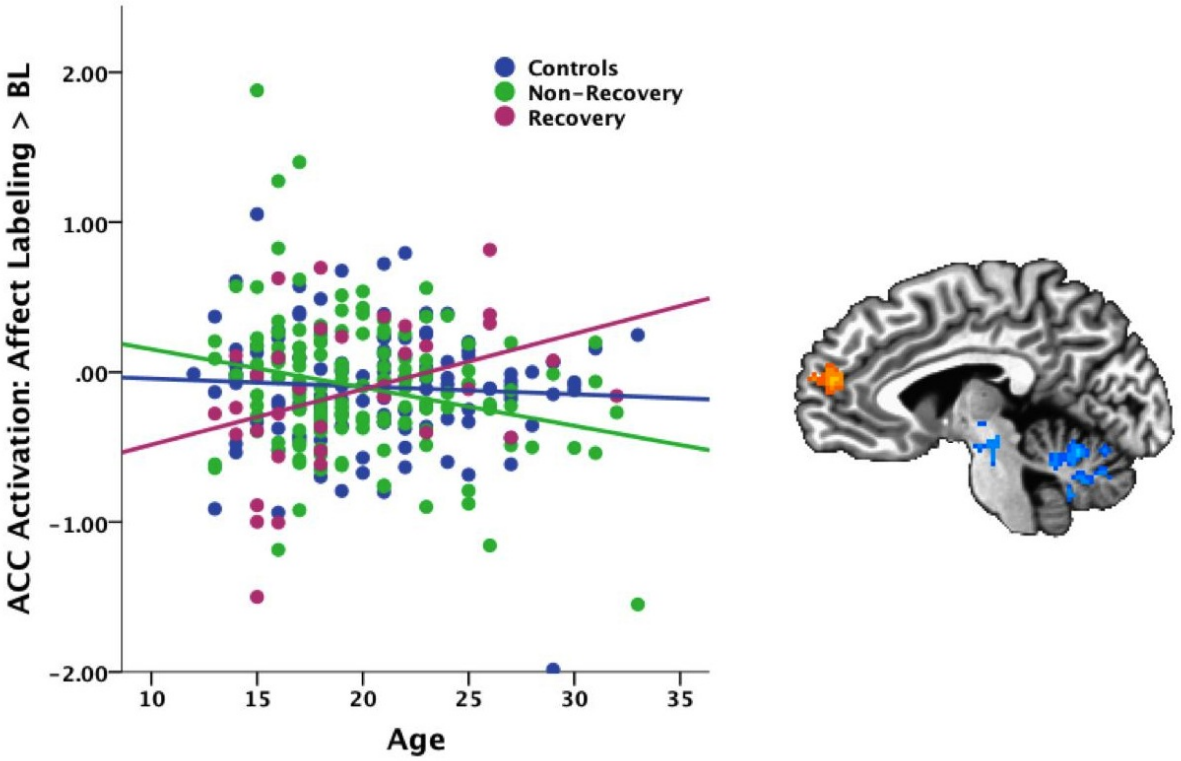


Figure 22. Age-Related Functional Connectivity and Recovery. For affect labeling, the recovery group displayed age-related increases in activation in the ACC and medial frontal gyrus, which significantly differed from the lack of age-related change observed in the non-recovery and control groups (p=.0013 for ACC, p<.0001 for medial frontal gyrus; corrected).

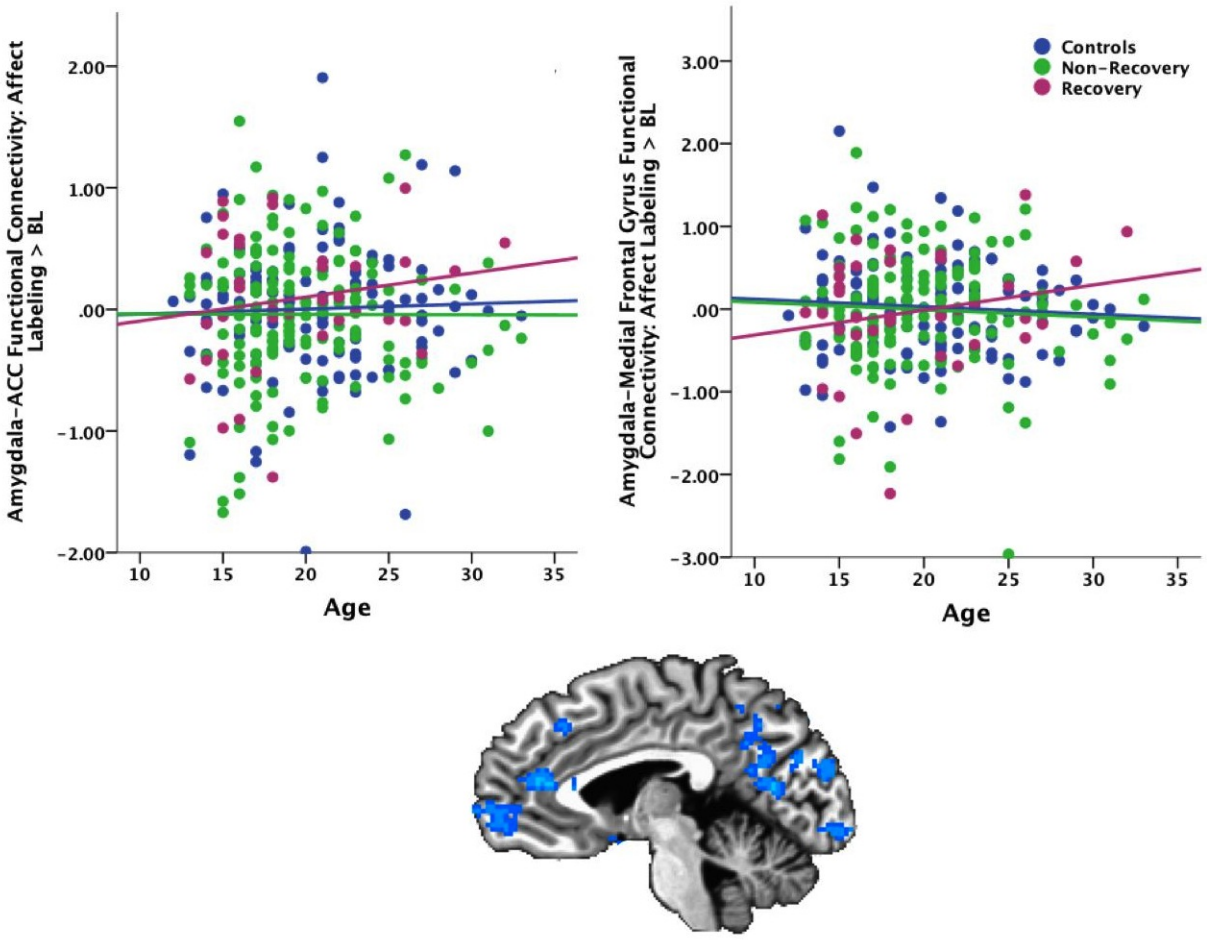
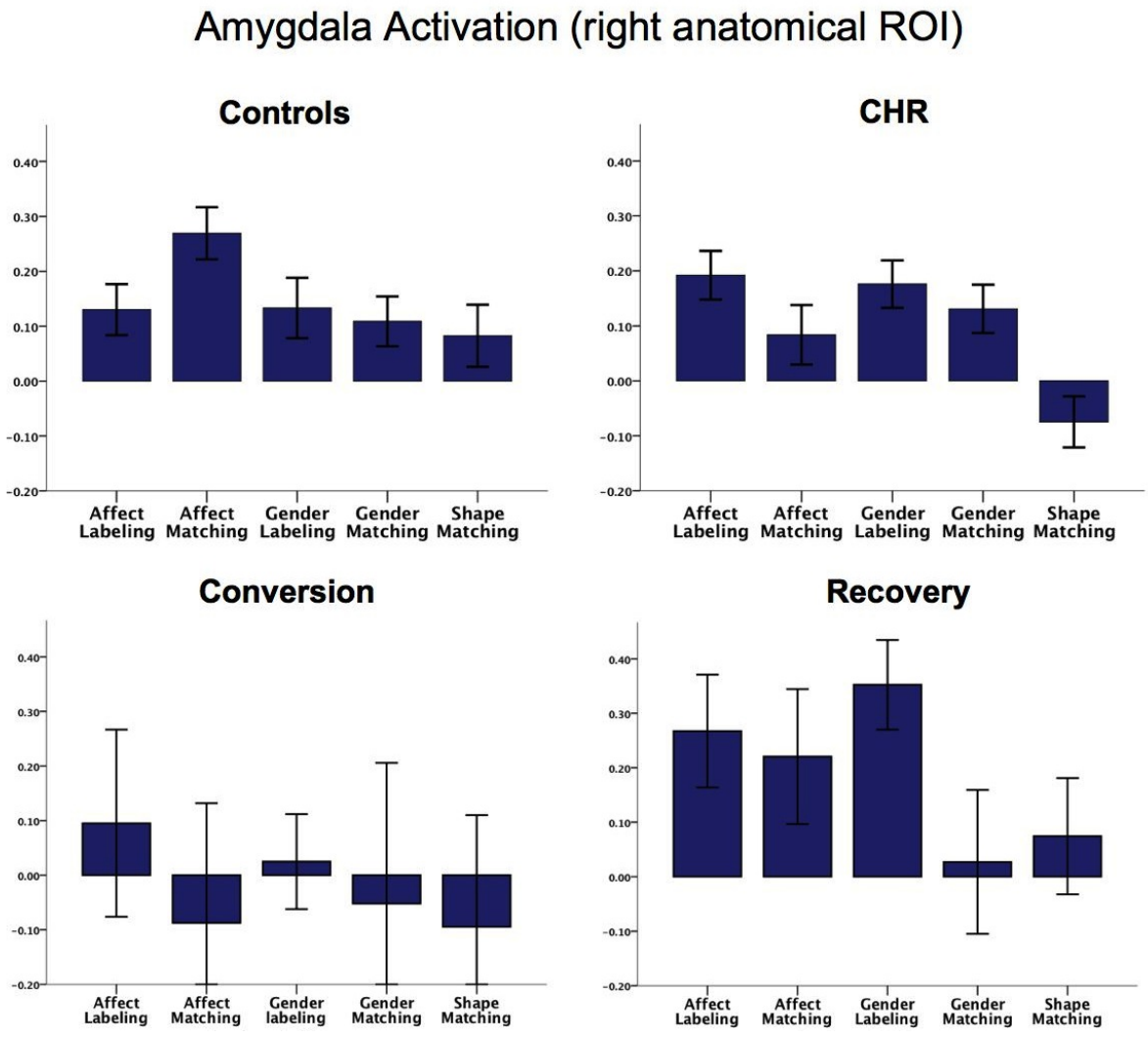


Figure 23. Amygdala Activation Within Groups. An analysis of amygdala activation (using an anatomically defined right amygdala mask) revealed that the CHR subgroups displayed unique patterns of activation to different task conditions. Controls displayed heightened amygdala activation for affect matching, with a decrease in amygdala activation during affect labeling. In contrast, the overall CHR group displayed a trend toward greater amygdala activation to affect labeling than affect matching (p=.075). Within the conversion and recovery groups, there were no differences in amygdala activation between affect matching and affect labeling.



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